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THE DILUTION CURVE OF ACTIVITY IN ARTERIAL BLOOD AFTER INTRAVENOUS INJECTION OF LABELED CORPUSCLES

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THE prolongation of the circulation time, determined by the decholin method in heart insufficiency, is not only an expression of the degree of stasis but also of the dilatation of the heart and thus of the residual blood in the heart.¹⁻⁴ In compensated cardiological cases there is a clear connection between the circulation time and the roentgenologic volume of the heart.³ In other words the greater the heart volume the longer its circulation time, a circumstance which is further illustrated by a more detailed statistical investigation of a large amount of material.⁵ It has also been possible to prove static, simultaneous changes in the amount of residual blood in the heart and in the circulation time.³ The connection, not previously observed, between the length of the circulation time and the amount of the residual blood in the heart explains observations made earlier, *inter alia*, by Weiss⁶ and Nylin and co-workers. In certain cases of heart insufficiency there was little or no change, i.e., shortening, in the circulation time in spite of the symptoms of insufficiency, and the stasis phenomenon yielded to therapy, which is explained by the fact that the dilatation of the heart persisted.

The circulation time is thus extremely dependent on the mixing conditions of the injected test substance in the heart cavities. I have shown earlier that, with the decholin method, not only the first taste sensation but at times also the duration of the sensation is an expression of the amount of the residual blood. In several respects, however, the decholin method is not satisfactory. A more detailed analysis of the afore-mentioned circulation phenomenon presupposes that a test substance which remains constantly attached preferably to the red blood corpuscles for a relatively long space of time can be introduced into the circulating blood and subsequently analyzed with satisfactory exactness on blood specimens. The test substances which have been employed in recent times, such as certain dye substances, vital red and, above all, "Evans Blue" T-1824, carbon monoxide, and certain other substances, such as decholin, histamine, saccharin, and lobeline lack, more or less, these afore-mentioned prerequisites. By the method of Hevesy and his co-workers.⁷⁻⁹ i.e., labelling the red blood corpuscles with radioactive isotopes, in the first place ³²P, a

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new field was opened up for circulation research. In a preliminary work Nylin and Malm¹⁰ showed that this method of labelling and subsequent analysis is applicable to investigations into the mixing conditions in cases of different amounts of residual blood in the heart. Hevesy and others¹¹ have applied the method for determining the circulating blood volume in healthy persons, and they discuss in detail the sources of error from which this method may conceivably suffer. How uniformly the radioactive phosphorus is attached to the red blood corpuscles appears to be of the greatest significance. From the investigations of Hevesy and his co-workers it seems to emerge that the chances of radioactive phosphorus infiltrating into the blood corpuscles from the radioactive plasma are many times greater than those of radioactive phosphorus being expelled from the blood corpuscles into the plasma, but on the other hand that the resorption from the plasma of the radioactive phosphorus through the capillary wall is extremely rapid. Even if allowance is made for the error of the method, due to some active plasma being left with the decentrifuged red blood corpuscles, when the activity of the different specimens is determined, the total error ten minutes after the injection appears to amount to only 0.5 per cent. From my investigations it appears that relatively constant values of the activity are still obtained twenty minutes after the injection of the labelled blood corpuscles.

From what has been said it emerges that Hevesy's method affords possibilities of studying certain circulation phenomena with greater exactness than earlier methods afforded and satisfies the prerequisites for analyzing more closely the connection between the magnitude of the residual blood in the heart and the circulation time. It appeared that the decholin times were correlated with the type of the dilution curve of the activity in the arterial blood.

For the purpose of studying more thoroughly and of throwing light upon the afore-mentioned observations, the investigations were extended to comprise both normal cases and certain cardiological cases.

METHOD

On the whole, the procedure described in the first published work was followed.¹⁰ As a rule we took 6 c.c. of blood from the patient in the morning by means of venous puncture. This was put into a paraffined flask containing approximately 0.3m C radioactive phosphorus. The flask was then shaken in a thermostat at 37° C. for two hours. Half the labeled blood, i.e., 3 c.c., was then injected into a vein in one of the patient's arms. The injecting was carried out rapidly during the course of one to two seconds. The patient lay in a horizontal position and quite still during the experiment. Before the injection of the labeled blood corpuscles, a puncture of the *arteria brachialis* of the other arm was made, and a specimen-taking cannula, fitted with a tap, was inserted.

Fractioned specimens were then taken and collected in small glass tubes immediately after the intravenous injection of the labeled blood corpuscles. The times of the specimen taking (as shown by stop watches) are accurately given in seconds after the injection. The remainder of the labeled blood corpuscles which were not injected and the various fractioned specimens were dealt with in the manner described in an earlier work, and finally the activity was determined for each specimen with the Geiger counter. First, the activity is

given by the number of impulses per gram of blood corpuscles, i. e., the specific activity, and second, the activity of the different specimens is expressed as a percentage of the most strongly labeled specimen, i.e., the relative activity. Further, for all the healthy experimental persons and for the patients, measurements were made of the venous pressure. The circulation time was determined by the decholin method, and the roentgenologic heart volume was determined. In determinations of the heart volume the method which has previously been published was employed.¹²

RESULTS

The material comprised five experimental persons who were healthy from the point of view of circulation, and six persons with heart disease, the latter consisting of five without signs of heart decompensation, and finally, one with typical heart insufficiency and cardiosclerosis. This patient had been followed with repeated circulation investigations over a long period, until, after appropriate therapy, all signs of insufficiency had disappeared. The five compensated heart cases comprised one instance of aortic insufficiency (Case 6), an instance of combined mitral stenosis and aortic insufficiency (Case 7), an instance of cardiosclerosis (Case 8), an instance of hypertonia (Case 9), and, finally, an instance (Case 10) of operated concretio cordis. A survey of all the cases is given in Table I, containing the most important data as to the heart volumes, circulation times, and venous pressures.

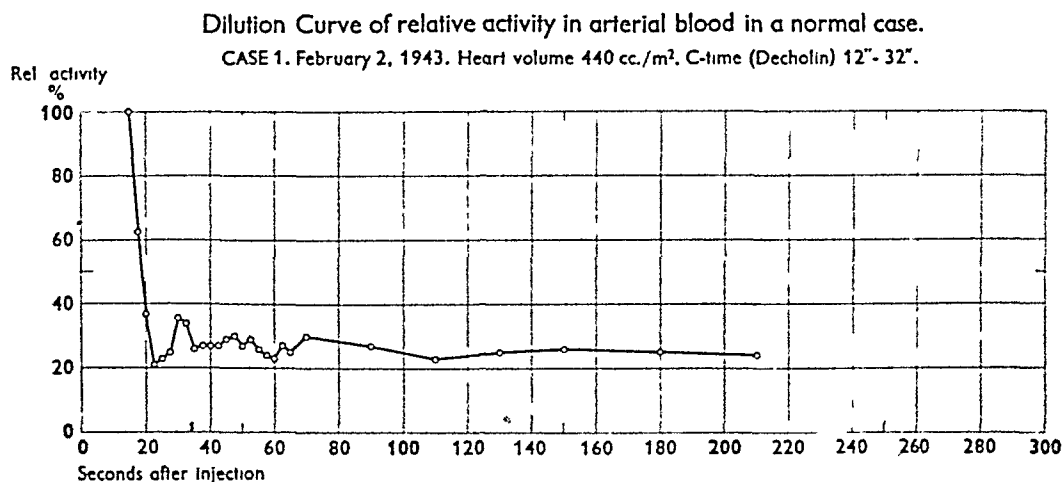


Fig. 1.

The material is not large, but owing to the considerable number of the fractionated specimens—in each case between 30 and 40—and the time-consuming method of ashing the specimens, it has not yet been possible to investigate a larger number.

It appears from Table I that all the heart volumes in the healthy persons were within normal limits. The upper limit for the normal, according to what has been indicated earlier, is 500 c.c./m² of body surface. The circulation times determined with decholin are short and within normal limits. Thus, on an average, the first taste sensation was perceived after fourteen seconds, and the bitter taste disappeared after thirty-two seconds. The first figure agrees with the mean value of twelve seconds observed on a considerable normal material in an earlier work. The means figure for the cessation of the taste sensation is higher than the corresponding figure of twenty-five seconds in the last-mentioned work.

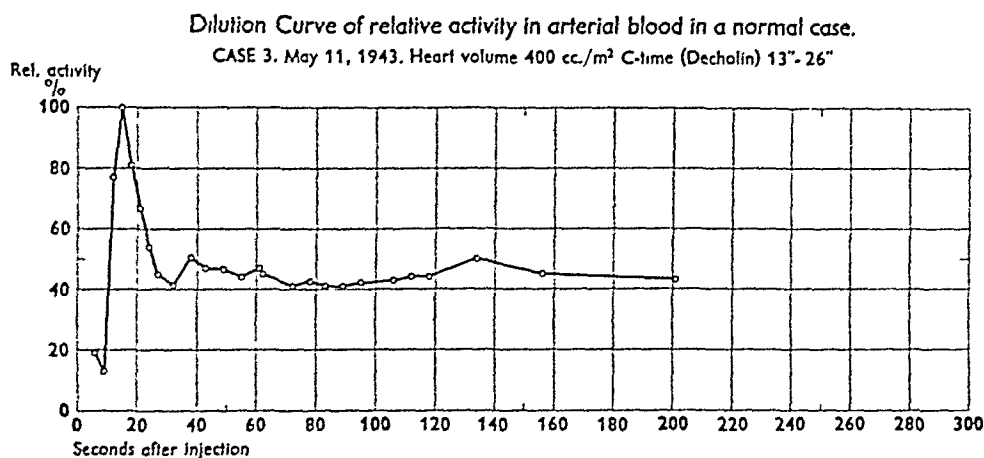
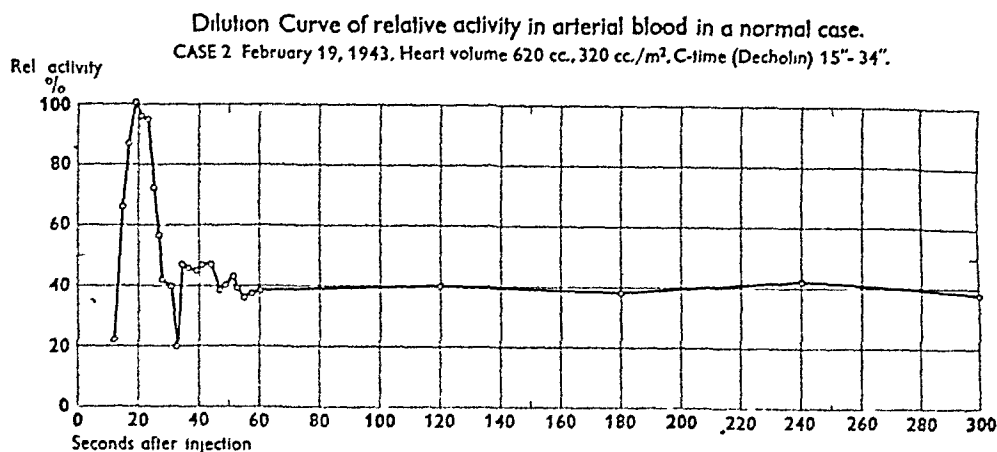


TABLE I

	CASE	DATE	DIAGNOSIS	VENOUS PRES- SURE (CM.)	HEART VOLUME		CIRCULATION TIME (DECHOLIN) (SEC.)	
					(C.C.)	(C.C./M ²)	FIRST SENSA- TION	LAST SENSA- TION
Normal cases	1	Feb. 9, 1943				440	12	32
	2	Feb. 19, 1943			620	320	15	34
	3	May 11, 1943				400	13	26
	4	Oct. 11, 1942			880	450	12	25
	5	Feb. 8, 1944			978	500	17	42
Mean						422	14	32
Compensated heart cases	6	March 30, 1943	Aortic regurgita- tion?	13	1480	750	14	30
	6	May 25, 1943	Aortic regurgita- tion?	14	1470	785	16	30
	7	June 9, 1943	Mitral stenosis and aortic re- gurgitation	11	1460	820	17	30
	7	(July 14, 1943)	Mitral stenosis and aortic re- gurgitation	(8)	1680	970	22	65
	8	June 22, 1943	Cardiosclerosis	5	(1470)	(860)	(20)	(45)
	9	March 16, 1944	Hypertension	13	1480	830	32	83
	10	June 12, 1944	Constrictive peri- carditis	10	2100 820	1200 470	37 13	85 29
Mean						851	24	59
Decompensated heart cases	11	May 15, 1944	Cardiosclerosis	17	1610	895	35	65
	11	May 25, 1944	Cardiosclerosis (compensated)	5	1350	845	21	44

The dilution curves for the relative activity in the arterial blood in the normal cases is shown in the diagrams, Figs. 1, 2, 3, 4, and 5. From these it appears that there is good agreement between, first, the different normal cases, and second, the dilution curves for the radioactive labeling and the decholin times. Equilibrium appear fairly rapidly, as is shown in the diagram, sometimes after about sixty seconds and, as a rule, during the second minute after the intravenous injection. Similarly it appears that the activity remains strikingly constant during the following four minutes, and in one normal person (Case 5) it remained relatively constant up to fifteen minutes after the injection, as is shown by Fig. 5. In another case, simultaneously fractionated specimens were taken from both arterial and venous blood, beginning at the second minute after the injection of the labeled blood corpuscles. In Table II will be

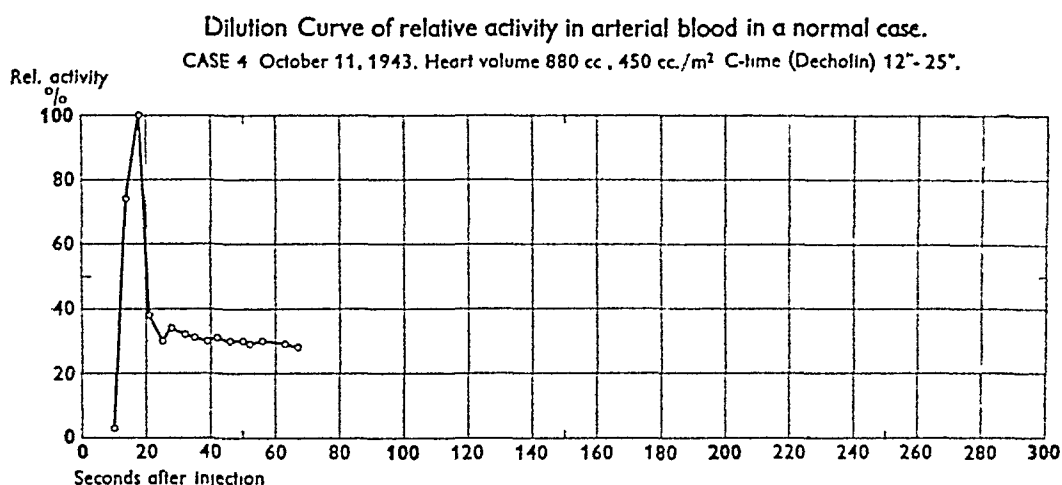


Fig. 4.

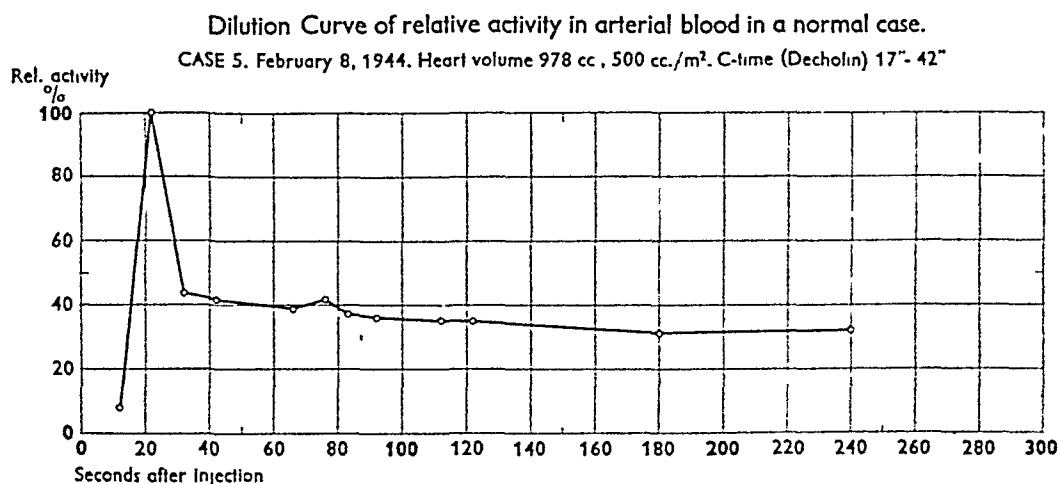


Fig. 5.

found the values for the specific activity, which prove to be relatively constant from the second up to and including the twenty-first minute after the injection. There is remarkable agreement between the values of the arterial and venous specimens. It is very important to know more exactly how long the activity remains constant in the blood and to study more in detail the decrease in activity some considerable time after the injection. In one case the specific activity in the venous blood was determined several days in succession, and this gave the result that after 48 hours the specific activity of the red blood corpuscles had fallen by 44 per cent, after 72 hours by 60 per cent, after 144 hours by 85 per cent, and after 168 hours by 93 per cent of the equilibrium value.

As has been mentioned previously and as emerges from the tables, the pathologic heart cases comprised five compensated cases and one typical case of heart decompensation. The heart volumes in the compensated cases are very large as a rule, with the exception of one case of concretio cordis which was freed by an operation from its chronic heart tamponade. The mean value of the five heart volumes amounts to 851 c.c./m² of body surface, i.e., double the value for that of the normal heart cases. On an average, the circulation times determined with decholin were, for the first taste sensation, 24 seconds, and for the last taste sensation, 59 seconds. Thus, in spite of the absence of stasis the

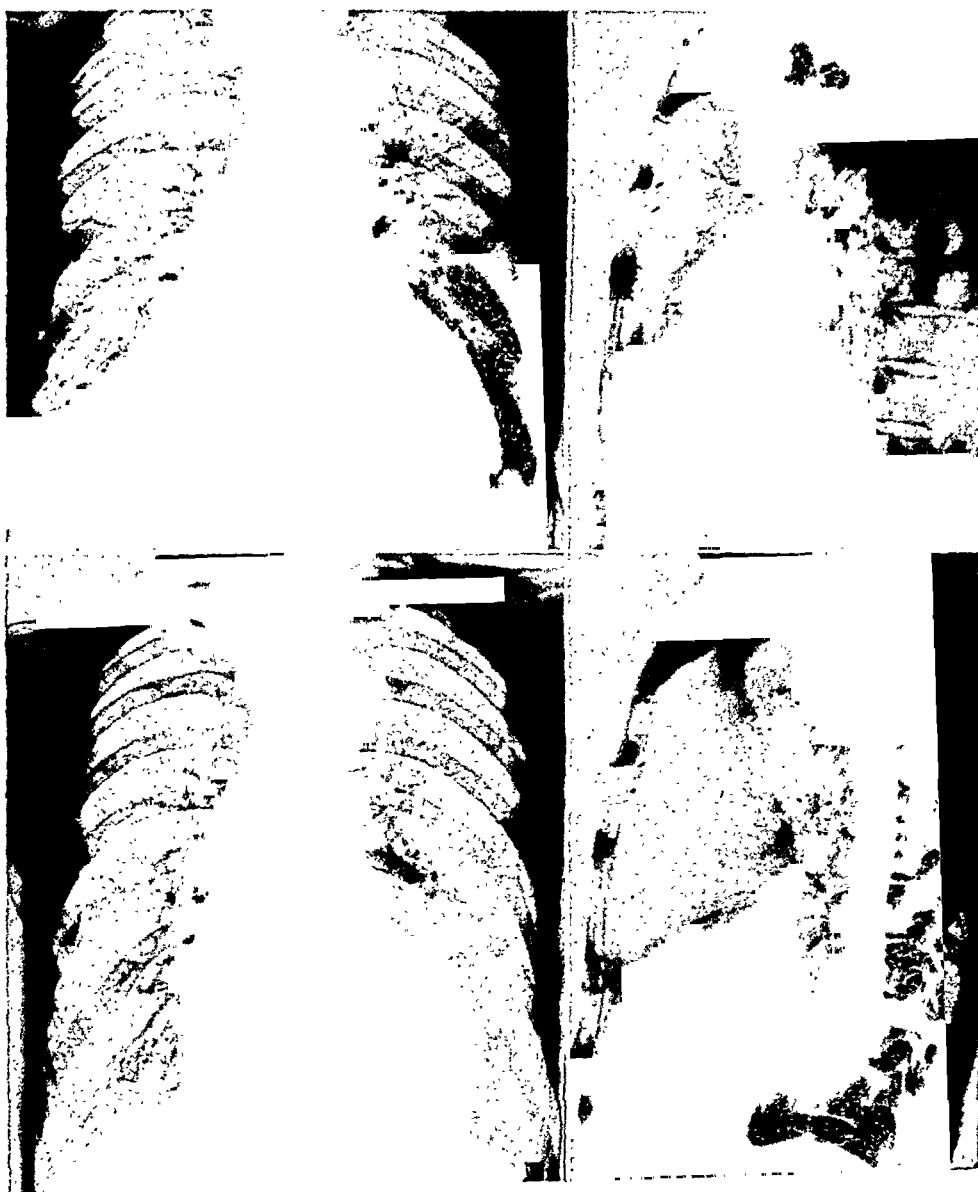


Fig. 6.—Case 11. Decompensated cardiosclerosis. After treatment, heart volume decreased 260 cubic centimeters.

circulation times are nearly twice the normal. Case 10, with a normal-sized heart, exhibits normal circulation times. Entirely contrary to my experience, i.e., that long circulation times are met with in cases of heart dilatation and large amounts of residual blood, Case 6 exhibited remarkably short and completely normal circulation times after repeated controls, an interesting circumstance which will be discussed more in detail later. Finally, on admission to the clinic, the last case, Case 11, showed the typical picture of grave heart decompensation in a 61-year-old man with cardiosclerosis. He exhibited diffuse

TABLE II

TIME AFTER INJECTION (MIN.)	SPECIFIC ACTIVITY (IMPULSES PER GRAM PER MINUTE)	
	ARTERIAL BLOOD	VENOUS BLOOD
2	161	
6	159	159
8	162	162
14	149	155
17	150	150
19	150	159
21	159	159
Mean	155	157

Dilution Curve of relative activity in arterial blood in a case of aortic regurgitation?

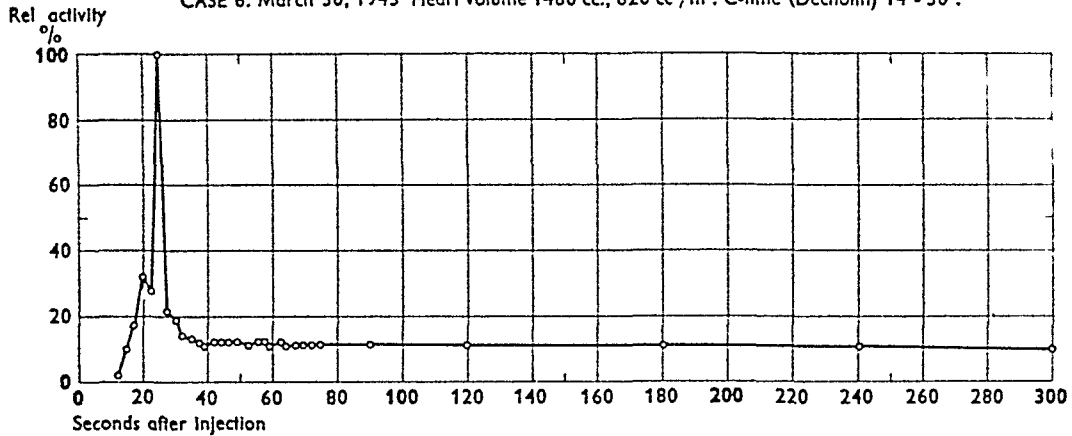
 CASE 6. March 30, 1943 Heart volume 1480 cc., 820 cc./m². C-time (Decholin) 14"-30".


Fig. 7.

Dilution Curve of relative activity in arterial blood in a case of aortic regurgitation?

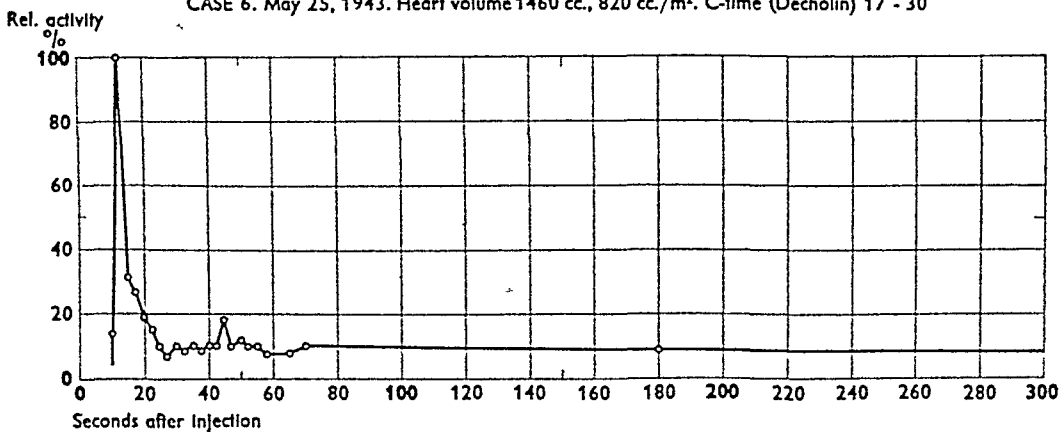
 CASE 6. May 25, 1943. Heart volume 1460 cc., 820 cc./m². C-time (Decholin) 17"-30"


Fig. 8.

edema over the legs, thighs, and up across the back; the liver was palpated a handbreadth below the costal margin, and, on the day of admission, the venous pressure reached a very high value, 25 centimeters. Some days later, on May 15 (see Table I), when the special examinations were made, it had fallen to 17 centimeters. The heart was strongly dilated and the heart volume greatly enlarged, namely 895 c.c./m² of body surface. The circulation times were markedly long, 35 and 65 seconds, respectively. After treatment with digitalis and diuretics, all the stasis phenomena and the edema disappeared, resulting in a decrease in weight of 10 kilograms. At the same time the circulation times were certainly shortened to 21 and 44 seconds, respectively, for the first and last taste sensations, but did not quite return to normal values. Simultaneously with the decrease in the circulation times the heart volume decreased very considerably, by nearly 300 cubic centimeters. The roentgenologic decrease in volume appears in Fig. 6.

TABLE III

TIME AFTER INJECTION (DAYS)	DECREASE IN ACTIVITY AS PERCENTAGE OF MIXING VALUE
2	44
3	60
6	85
7	93

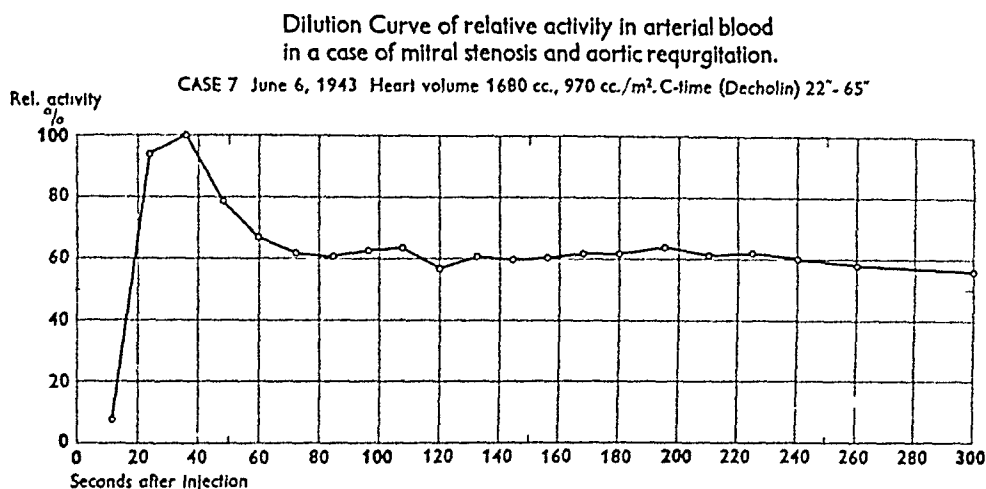


Fig. 9.

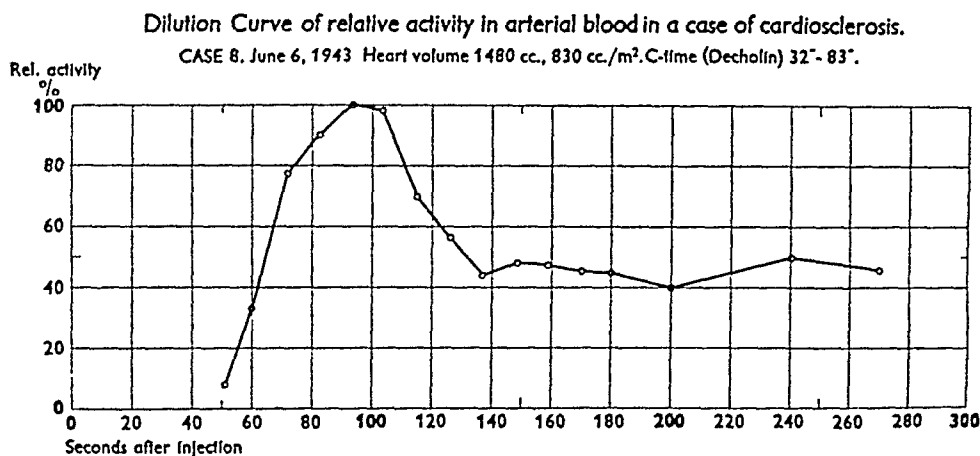


Fig. 10.

Figs. 7, 8, 9, 10, 11, 12, 13, and 14 are the dilution curves of the relative activity in the fractionated specimens from arterial blood after intravenous injection of labeled blood corpuscles. As we have found, the courses of these curves for the five compensated heart cases diverge greatly from those of the normal cases, with the exception of Case 6 (Figs. 7 and 8), a case of aortic insufficiency, and the operated case of concretio cordis (Case 10, Fig. 12). The latter has a normal heart volume, a normal dilution curve and normal circulation times. Cases 7, 8, and 9 (Figs. 9, 10, and 11) have large heart volumes and long circulation times measured by the decholin method, and in complete agreement with this the activity reaches the maximum successively and late, and then gradually and late reaches the state of equilibrium. As a rule it takes several minutes before equilibrium is attained. In Case 9 (Fig. 11) equilibrium does not appear to be reached before the seventh minute.

Case 6 was subjected to control determinations on a later occasion even with decholin. The two dilution curves (Figs. 7 and 8) show particularly consistent results and remarkable agreement with the curves for the normal cases

in spite of the fact that the heart volume is considerably enlarged, and there is reason to assume the presence of large amounts of residual blood. On several occasions, in complete conformity with the normal type of dilution curve, the decholin times have proved to be entirely normal. The explanation of the re-

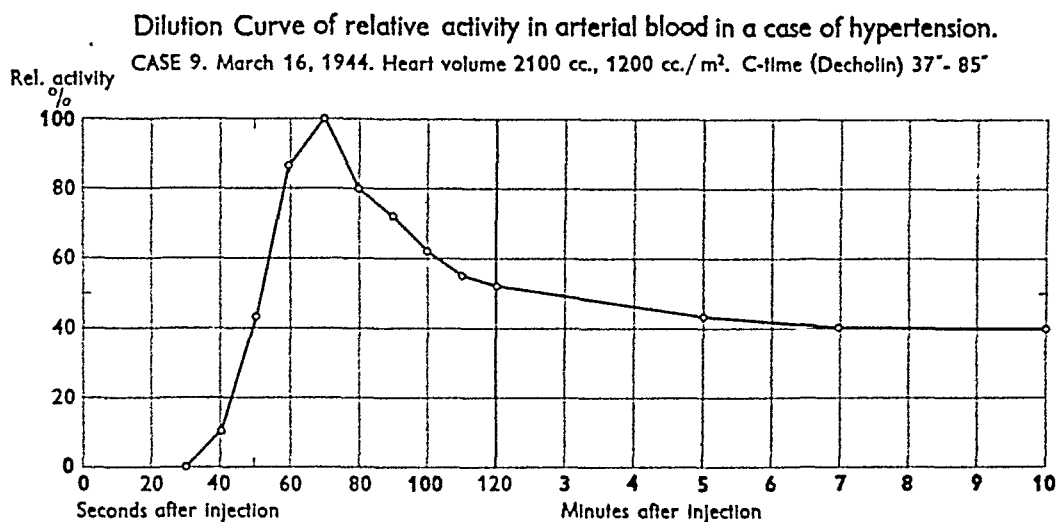


Fig. 11.

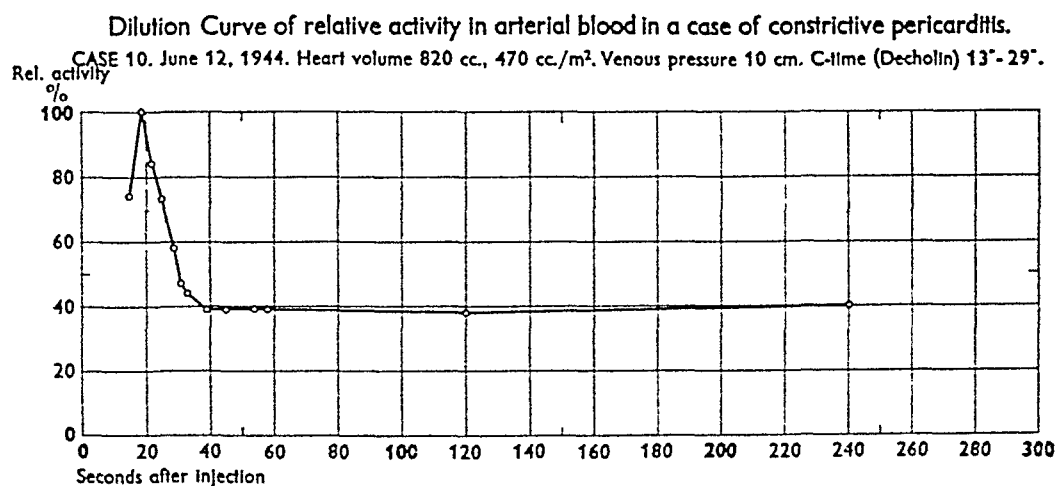


Fig. 12.

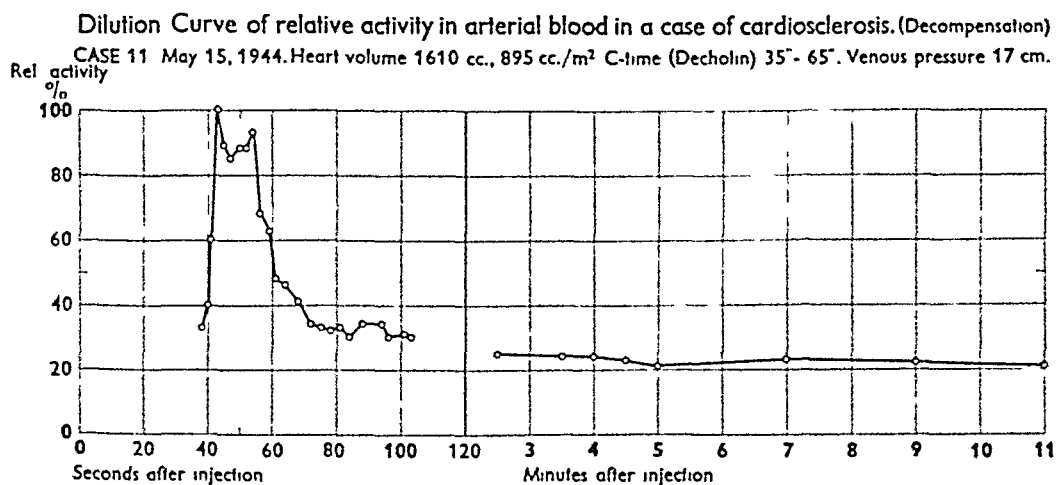


Fig. 13.

markable conditions in this exceptional case cannot be indicated with certainty. Possibly there was a defect in the ventricular septum with a dilated heart, which explains the short circulation times and the fact that the dilution curve with the radioactive labeling of the red blood corpuscles is normal.

Finally, we come to the last case, a typical heart insufficiency, which at the first examination (Fig. 13) had a high venous pressure of 17 cm., a large heart volume of 1,610 c.c., and pathologically long circulation times. Here the dilution curve is in complete agreement with those of the compensated cases with large heart volumes. Equilibrium appears late in this case, too, not before the fifth minute after the injection. Ten days later, when complete compensation had appeared, the type of curve certainly changes appreciably (Fig. 14) and to some extent approaches that of the normal cases; nevertheless the pathologic type persists. Not until the third minute is equilibrium attained. On the occasion of the last examination the circulation times also were clearly and pathologically prolonged, and at the same time the heart volume had certainly decreased but still remained considerably enlarged.

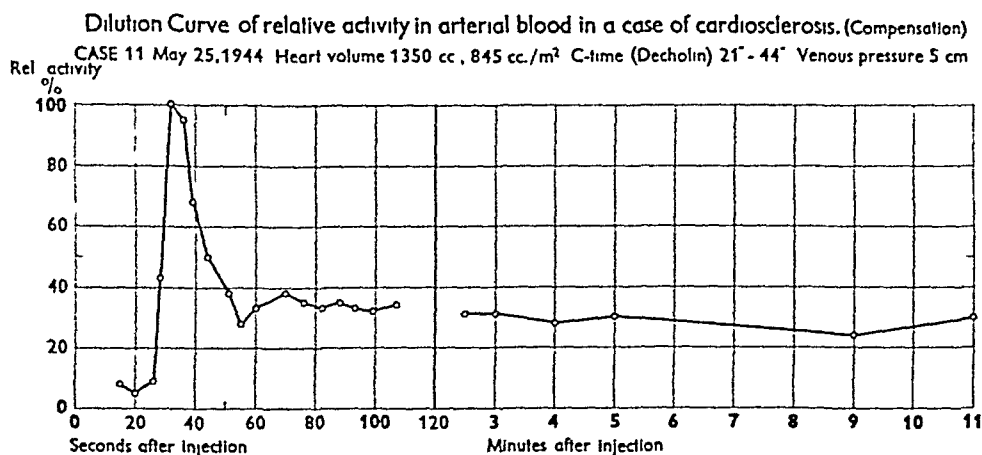


FIG. 14.

SUMMARY

Red blood corpuscles from the experimental person labeled with radioactive phosphorus were injected intravenously into the same individual, after which the activity on fractioned specimens from arterial blood was determined by means of a Geiger counter. In this way a dilution curve was obtained which appeared to be characteristic of healthy experimental persons in whom both the initial rise and the return to the position of equilibrium takes place rapidly. In pathologic heart cases with large amounts of residual blood in the heart, this dilution curve is of a completely different type, with a slow gradual rise to a maximum for the activity and subsequently a slow gradual falling part, where equilibrium is gradually reached.

There appears to be an obvious connection between the circulation times determined by the decholin method and the type of dilution curve, on the other hand and between the dilution curve and the size of the heart and the amount of the residual blood on the other. It is extremely probable that the prolonged circulation time in cases of heart insufficiency is not, as has previously been assumed, due to stasis only, but to a great extent, possibly chiefly, to the dilated heart and thus to the amount of residual blood.

For determinations of the circulating blood volume in cardiological cases it appears to be necessary to know the course of the dilution curve.

I beg to extend my warm thanks to Professor G. von Hevesy for his unfailing interest, and to Professor Manne Siegbahn, who kindly placed radioactive phosphorus at my disposal. I owe grateful thanks to Licentiate M. Malm and Professor Runnström for help with certain

of these investigations. My assistant, Miss Ingrid Larsson, has helped me indefatigably in the work, and my gratitude is also extended to the Therese and Johan Andersson Memorial Fund for a grant which made this investigation possible.

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CHANGES IN THE PRECORDIAL ELECTROCARDIOGRAM PRODUCED BY EXTENSION OF ANTEROSEPTAL MYOCARDIAL INFARCTION

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THIS report is concerned with an electrocardiographic study of two patients, each of whom experienced two attacks of severe anginal pain within a short period of time. The observations made suggest that in each case the first attack was associated with the development of a small anteroseptal myocardial infarct, whereas the second attack was related to the lateral extension of the initial lesion. The electrocardiograms illustrate the value of multiple precordial leads in the diagnosis of this sequence.

CASE REPORTS

CASE 1.—A 43-year-old housewife was admitted to the University Hospital on Aug. 6, 1943. On the morning of the day of admission to the hospital, about one hour after awakening, the patient noted mild precordial oppression which cleared spontaneously. It recurred about one hour later and became increasingly severe. Numbness in both shoulders, pain radiating to the left arm and hand, and a mild sense of suffocation developed. When examined by her physician shortly after the onset of these symptoms, the blood pressure was 160/120. Inhalation of amyl nitrite and two doses of morphine sulfate of 0.016 Gm. ($\frac{1}{4}$ grain) each, subcutaneously, gave no immediate relief. She was admitted to the hospital a few hours later.

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There was no history of previous complaints referable to the heart. The patient had been examined in the outpatient clinics on several occasions. The blood pressure was recorded as 128/100 in January, 1939, 160/110 in November, 1941, and 150/90 in March, 1942. Her father died of angina pectoris. Her mother had an abnormally high blood pressure, but died of a perforated ulcer.

Physical Examination.—When first seen, the patient was somewhat pale and drowsy. She was not complaining of pain, possibly because the opiates which had been administered at her home had become effective. The temperature, pulse rate, and respiratory rate were normal. The heart sounds were of good quality and the cardiac rhythm was normal. The blood pressure was 118/80. The remainder of the physical examination was negative.

Laboratory Data.—The blood, urine, and blood serologic examinations were negative. The leucocyte count rose from 9,300 on admission to 11,850 on the fourth hospital day, and then returned to normal. The sedimentation rate on admission was 36 mm. per hour (Wintrobe method). Subsequent determinations were 0.8 mm. per minute on September 14, 0.96 mm. per minute on September 24, and 0.4 mm. per minute on February 4, 1944 (Ernstene and Rourke method).

Clinical Course.—The usual treatment for myocardial infarction was instituted. Except for occasional palpitation, the patient was quite comfortable during the first thirty-six hours. On the evening of August 7, precordial distress recurred, and, in the early morning hours of August 8, it became quite severe, with radiation to both arms. The pain persisted with variations in intensity for thirty-six hours. During this period, four doses of morphine sulfate of 0.016 Gm. ($\frac{1}{4}$ grain) each, and then five doses of dilaudid of 0.002 Gm. ($\frac{1}{30}$ grain) each, were administered. The patient grew pale, restless, and somewhat confused. She was kept in an oxygen tent for eight days. The temperature, which had been normal during the first two days, rose to 101.2° F. (R), and the pulse rate, to 116 per minute. The respiratory rate fell to 5 per minute. The blood pressure remained at about the same level as on admission. After the eighth hospital day there was progressive improvement, and convalescence was uneventful except for a mild upper respiratory infection. The patient was discharged on the fifty-second hospital day. When last seen, on Sept. 23, 1944, she was feeling well except for mild sciatica, and had been able to resume nearly full, normal activity.

Electrocardiograms.—The standard leads and unipolar extremity leads taken on August 6, six and one-half hours after the onset of symptoms, show slightly inverted T waves in Lead I and sharp terminal inversion of the T waves in Lead V_L (Fig. 1). Although somewhat suggestive, these records are not diagnostic of myocardial infarction because there are no significant changes in the QRS complexes. The precordial leads taken on August 7, twenty-seven hours after the onset of symptoms, show QS deflections in Lead V_2 and sharp terminal inversion of the T waves in Leads V_1 , V_2 , V_3 , V_4 , and V_6 (Fig. 2). These changes are characteristic of recent anteroseptal myocardial infarction. Infarcts in this location are usually not accompanied by diagnostic alterations in the standard limb leads.¹

The standard and unipolar extremity leads on August 9 (not reproduced), thirty-six hours after the recurrence of pain, are quite different from the first electrocardiograms. Prominent Q waves, small or absent R waves, and upward displacement of the RS-T segment are seen in Leads I and V_L , together with downward RS-T displacement in Lead III. The same changes are present in the tracings taken on August 11, except that displacement of the RS-T segment is more striking (Fig. 1). The precordial leads taken on this same date show large QS deflections in Leads V_1 , V_2 , V_3 , and V_4 and pronounced RS-T displacement in Leads V_1 , V_2 , V_4 , and V_6 (Fig. 2). Since the cavity potential (QS deflection) is now recorded not only in Lead V_2 but from several other precordial regions, chiefly to the left of this point, it is evident that the original zone of infarction had extended laterally. The RS-T displacement also suggests that further acute injury had occurred.

Standard, unipolar extremity and precordial leads taken on Sept. 9 display the expected progression of changes in the ventricular complexes (Figs. 1 and 2). The displacement of the RS-T segment has disappeared, and the T waves are now sharply inverted in Leads I, V_L , V_2 , V_3 , V_4 , and V_6 . Subsequent electrocardiograms, taken on Feb. 3 and July 7, 1944, are similar except that the changes in the T waves have regressed to some extent.

CASE 2.—A 53-year-old foreman was seen in the Heart Station on March 2, 1943. He was complaining of attacks of pressing, squeezing discomfort beginning in the right arm, extending to the upper right anterior part of the thorax and sternum, and occasionally to the right cervical region. The first attack occurred on Feb. 13, 1943, while he was sawing

wood. However, subsequent attacks were not closely related to exertion, and the pain awakened him frequently at night. The discomfort usually lasted five to thirty minutes. Nitroglycerin had been found to give relief. During the evening of March 1, he had five attacks of short duration.

In 1940, he had a transient left hemiparesis during an attack of "food poisoning." The blood pressure was found to be slightly elevated at that time. He had inflammatory rheumatism at the age of 3 years, and a gastroenterostomy for peptic ulcer at the age of 39 years. His father died of a "heart attack."

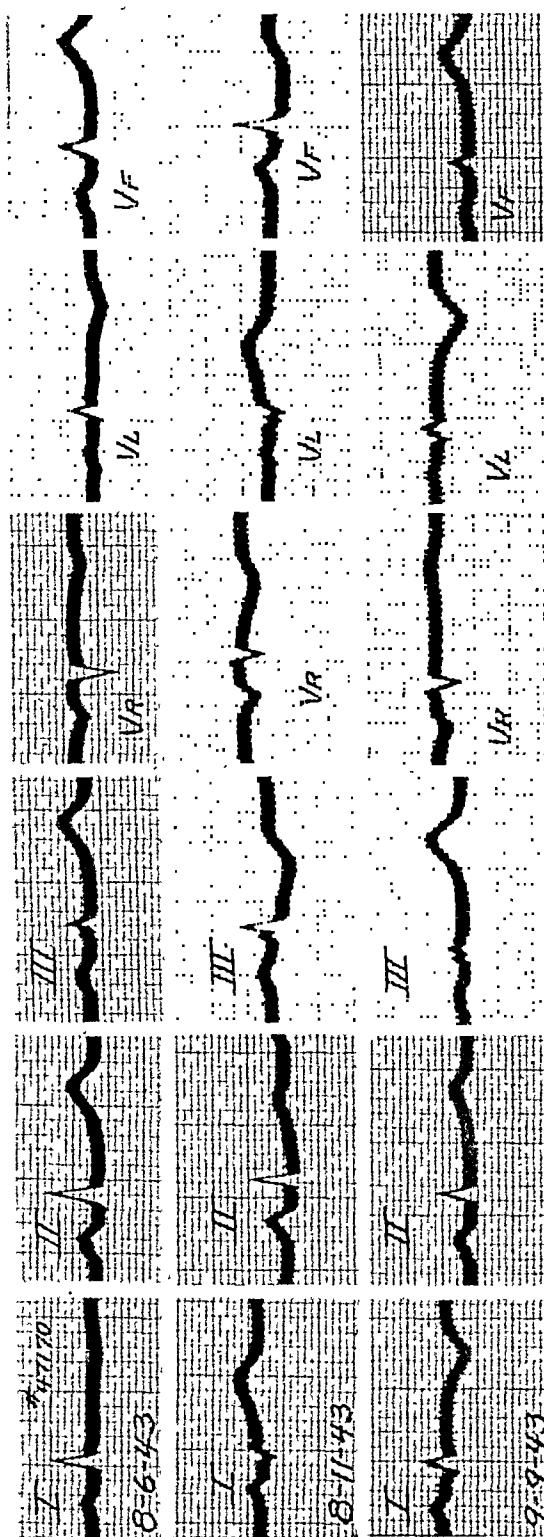


Fig. 1.—Case 1. Aug. 6, 1943: Standard leads and unipolar extremity leads taken six and one-half hours after onset of symptoms. Aug. 11, 1943: Standard and unipolar extremity leads four days after second attack. Sept. 9, 1943: Standard and unipolar extremity leads during convalescence.

Physical Examination.—The patient was a moderately obese, somewhat plethoric, middle-aged man. The heart was not enlarged. The aortic second sound was slightly accentuated. There were no murmurs or abnormalities of rate or rhythm. The blood pressure was 150/100. The remainder of the examination showed nothing of significance.

Laboratory Data.—The sedimentation rate was 9 mm. per hour (Wintrobe method). The miniature chest roentgenogram and the blood serologic reaction were negative.

Electrocardiograms.—The standard and unipolar extremity leads taken on March 2 show terminal inversion of the T waves in Leads I, II, and V_1 , i.e., changes suggestive, but not diagnostic, of recent myocardial infarction (Fig. 3). The precordial leads taken at the same time display prominent QS deflections in Leads V_1 , V_2 , and V_3 and deep terminal inversion of the T waves from all the precordial points explored (Fig. 3). These changes are characteristic of infarction of the anteroseptal portion of the left ventricular wall.¹

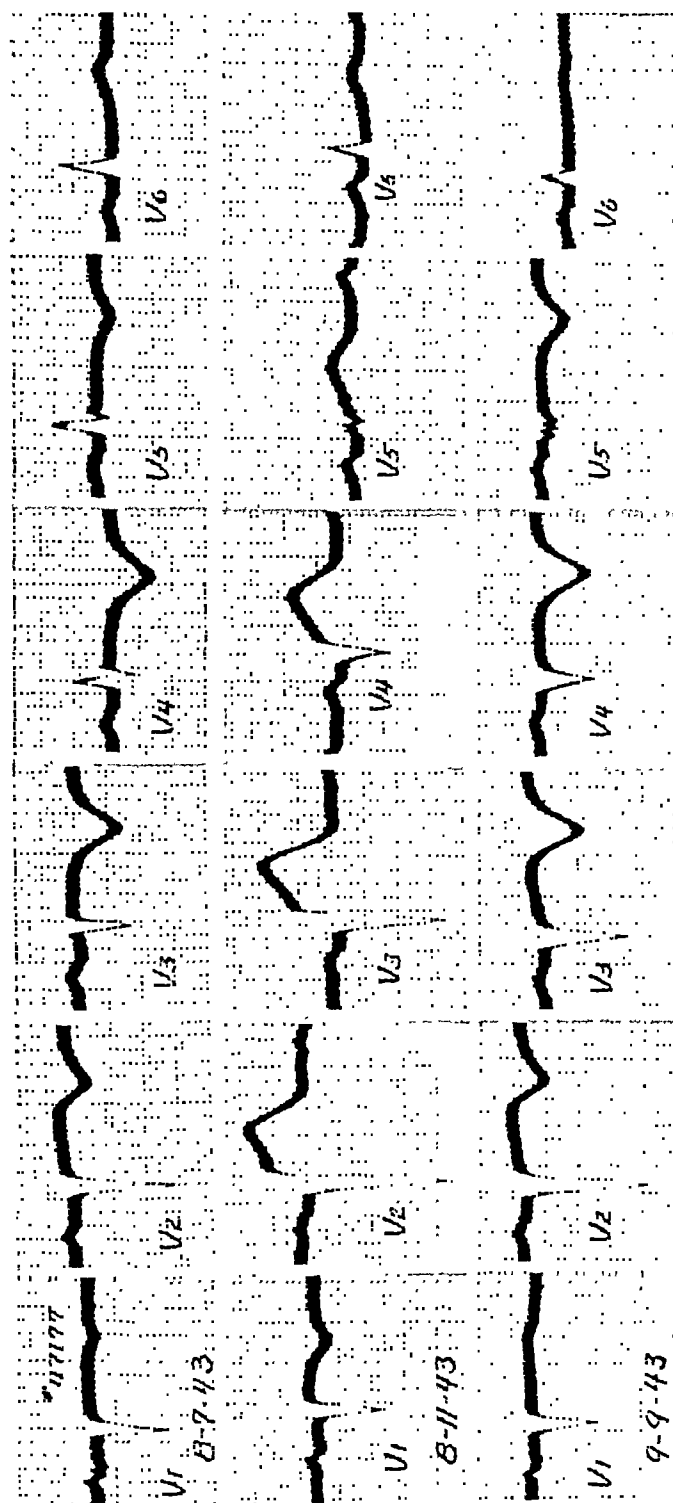


Fig. 2.—Case 1. Aug. 7, 1943: Precordial leads taken twenty-seven hours after onset of symptoms showing changes characteristic of recent anteroseptal myocardial infarction. Aug. 11, 1943: Precordial leads four days after second attack, showing evidence of lateral extension of the original lesion. Sept. 9, 1943: Precordial leads during convalescence, showing usual progression of changes.

Correlating these changes with the history, it seems probable that the infarction occurred during the preceding evening when the patient experienced the multiple, short attacks of anginal pain.

Second Admission.—After his first visit the patient was confined at home. On March 4, while in bed, he had an attack of pain in the right arm, thorax, and neck lasting eight hours. He took nitroglycerin tablets at intervals of five minutes (total of thirty tablets)

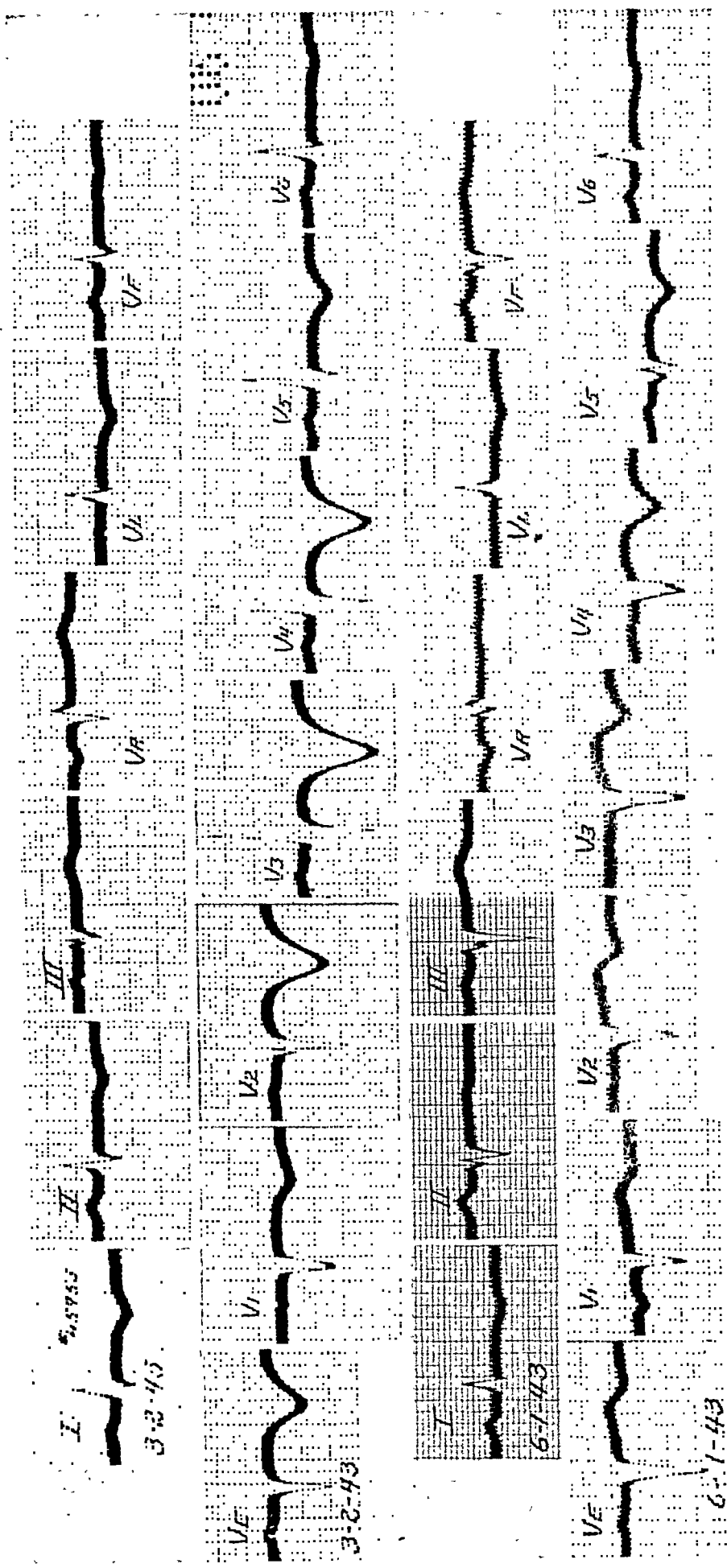


Fig. 3.—Case 2. March 2, 1943: Standard, unipolar extremity and precordial leads showing changes characteristic of recent anteroseptal myocardial infarction. Patient had five short, sharp attacks of anginal pain eighteen hours before, June 1, 1943; Standard unipolar extremity and precordial leads showing signs of the lateral extension of the initial infarct which probably occurred on March 4, 1943.

without obtaining relief. He remained in bed for five weeks and thereafter gradually resumed activity. He had no more prolonged attacks of pain, but mild anginal distress occurred on moderate exertion or excitement and was relieved by rest or nitroglycerin. He returned to the Heart Station for re-examination on June 1, 1943.

Physical Examination.—The findings were unchanged from those at the time of the first examination except that the heart sounds were rather faint. The blood pressure was 150/100.

Electrocardiograms.—Comparison of the standard and unipolar extremity leads taken June 1 with those recorded three months earlier discloses only minor changes. The R waves are smaller in Leads I, II, and V_F , the S waves are larger in Leads II, III, and V_F , and the T waves have become upright in Lead II (Fig. 3). The true significance of these changes becomes evident only when the precordial leads taken at the same time are examined (Fig. 3). QS deflections are now present in Leads V_1 , V_2 , V_3 , V_4 , and V_E . The T waves have become upright in Leads V_1 and V_E , but are again inverted in all the other precordial leads. A W-shaped QRS complex is now seen in Lead V_3 in which the initial ventricular complex was previously of normal form. It is evident that extension of the original antero-septal infarct laterally to involve the anterior and anterolateral regions of the left ventricle was responsible for these changes. The history suggests that this extension occurred on March 4, when the patient had the prolonged attack of anginal pain.

DISCUSSION

These two patients are quite similar with respect to their history and the character and sequence of development of the electrocardiographic changes. In each case, the initial infarct was associated with relatively minor clinical manifestations and only T-wave changes in the standard and unipolar extremity leads (Figs. 1 and 3). The precordial leads, however, show characteristic QRS and T-wave changes due to antero-septal myocardial infarction in the leads from the extreme right side of the precordium (Case 1, Fig. 2, Lead V_2 , and Case 2, Fig. 3, Leads V_1 , V_2 , and V_E). The full import of the initial clinical manifestations might have been overlooked if multiple precordial leads, and particularly leads from the right side of the precordium, had not been taken. This becomes still more apparent if Leads V_4 and V_5 of the records taken after the initial infarct are examined; these display only T-wave inversion, which, albeit pronounced, in the absence of QRS changes, does not permit an electrocardiographic diagnosis of myocardial infarction. Therefore, it can be seen that standard limb leads and single precordial leads from the region of the cardiac apex would not have been as helpful in these cases as tracings of the type reproduced here.

The even greater value of multiple precordial leads in these two cases is seen upon examination of the precordial electrocardiograms taken after the second attack of severe pain (Figs. 2 and 3). Since the changes in the QRS complexes are now recorded from a much larger area, it is evident that the initial zone of infarction has grown larger by lateral extension. Although one could have suspected from the clinical picture that an extension of the original infarct or a second infarct had occurred, the exact situation was not revealed until the multiple precordial leads were repeated. In Case 1, these records were made soon enough so that acute injury effects were also recorded (Fig. 2), thereby further substantiating the impression that additional muscle had been infarcted. This was not possible in Case 2 because the second set of records was not taken early enough to show such changes.

In Case 1, the standard and unipolar extremity leads also showed significant changes when the infarct extended, particularly in Leads I and V_L . This is usually the case in anterior and anterolateral infarction, for these leads ordinarily reflect the form of the electrocardiogram in Leads V_5 and V_6 . How-

ever, in Case 2, Leads I and V_L do not display changes of similar degree, although they do resemble Lead V_6 . This difference is probably due to a slight difference in the position of the heart in the two cases. That this is true is supported further by the fact that, after the extension of the infarct in Case 2, the QRS complex in the unipolar lead from the left leg (V_F) showed greater change than that from the left arm (V_L).

Several recent reports have pointed out that "premonitory" or "prodromal" symptoms may precede myocardial infarction.²⁻¹⁰ In both of the cases presented here, the symptoms accompanying the initial infarct were of the type which have been reported as frequently indicating "impending" infarction. Electrocardiograms taken on such patients during the interval between the onset of the prodromal symptoms and the occurrence of the myocardial infarct have usually been of normal form. However, in some of the records which have been published, there is inversion of the T waves in Lead I, in a single precordial lead, or in both, similar to that observed in the two cases reported here. On the other hand, in some cases of antero-septal infarction (as shown by leads from the right side of the precordium, V_1 , V_2 , and V_3), the standard leads and precordial leads from the region of the cardiac apex (V_4 , V_5 , and V_6) are well within normal limits.¹¹ Therefore, if multiple precordial leads had not been taken, thereby revealing that antero-septal infarction had already occurred, the two patients discussed here might also have been considered to have experienced only premonitory symptoms. The extension of the original lesion which occurred a few days later would then have been erroneously considered the initial infarction. The opinion that prodromal pain may actually be an expression of myocardial infarction in some cases has also been set forth by Dressler,¹² as well as by earlier observers.^{3, 8, 10}

Bayley¹³⁻¹⁵ has shown that the T-wave changes in patients with symptoms of impending infarction are the result of myocardial ischemia. He has presented important new evidence regarding the nature and manner of development of such changes. The alterations in the T waves which he has observed both clinically and in experimental animals are very similar to those recorded in the two cases presented here. However, the presence of significant QRS changes in the leads from the right side of the precordium in the records following the initial infarct indicate that, in addition to ischemia, actual infarction was present.

SUMMARY

Electrocardiographic studies are reported on two patients, each of whom had antero-septal infarction, followed in a few days by lateral extension of the initial lesion. The worth of multiple precordial leads in the diagnosis of extension of such infarcts is illustrated.

Evidence is again presented that infarcts which are antero-septal in location, as shown by diagnostic changes in leads from the right precordial area, often fail to produce equally significant changes in the limb leads.

It is suggested that, in cases of coronary arterial disease, some of the attacks of pain which have usually been considered prodromal symptoms of myocardial infarction, actually represent the development of a small, antero-septal infarct, and that the more characteristic symptoms of acute coronary thrombosis which often occur later are due to an extension of this initial lesion. The true situation must be recognized, if such patients are to be properly treated.

We do not wish to convey the impression that we are convinced that all attacks of so-called prodromal pain represent actual myocardial infarction. The data, at present available, bearing on this problem are inadequate to justify this conclusion. Some attacks of this character appear to be due to acute processes developing in the coronary arteries or to transient myocardial ischemia associated with such processes.⁷

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THE MEASUREMENT OF THE LUNG-TO-FACE TIME BY AMYL NITRITE

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STUDY of the velocity of the blood flow has been of practical value in the last decade only, during which period simple methods have been devised for timing the blood velocity in clinical practice, and have thus enabled this fundamental hemodynamic factor to be taken from the experimental laboratory to the bedside of the cardiac patient. The common basis of all clinical methods for measuring the blood velocity consists in the introduction of an active physiologic substance into the circulation by intravenous injection. Then the time is measured from the moment of injection until the appearance of characteristic effects, which differ, according to the agent employed, in various but always constant parts of the circulation, and that is the circulation time. The end point reaction can be of a subjective nature (heat, taste, smell) or objective nature (optical registration of its occurrence by a characteristic color change in certain parts of the circulation [fluorescein¹]; by a special detecting device if the substance employed is radioactive [radium C₂]; or by graphic registration if the provoked reaction is a cough or change in depth of breathing [lobelin,³ papaverine⁴]). From another point of view the clinical methods of measuring the circulation time can be divided into partial or total methods, according to the circulation zone involved. The total methods of measuring the blood velocity comprise the sum of part of the venous, the pulmonary, and a certain part of the arterial, circuits. The partial methods indicate it within one zone only. For example, the ether method (Hitzig⁵) gives information about the condition of the circulation in the venous half only, i.e., from the antecubital vein to the arterial capillaries of the lung.

Compared with the partial methods, the number of total methods of measurement of the circulation time is quite large. Among the former, the most frequently employed agents for the measurement of venous circulation are ether and paraldehyde.⁶ For the direct measurement of the lung-to-face time (apart from Gubner, Schnur, and Crawford's carbon dioxide method⁷), there are practically no other universally known procedures. In this paper, experiences with amyl nitrite as an agent for the direct measurement of the lung-to-face time will be described.

METHOD

The measurements were made on recumbent patients, after a rest period of ten minutes in a nonbasal condition. The amyl nitrite used in this study was obtained from ampules* which contain 4 minims of the drug and are covered by absorbent material. The time between the commencement of deep inspiration of the vapor of amyl nitrite and the appearance of a well-marked heat sensation in the face was registered by a centesimal chronometer, and represents the lung-to-face time as an expression of the trajectory from the pulmonary capillaries to the capillary bed of the face. Knowledge of certain peculiarities of the physiologic effects of breathing amyl nitrite vapors and adequate preparation of the patient for correct measurement are very important. Information must be given to lessen the possibility of nervous excitement before and during the process, in order to

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*Produced by Allen & Hanbury, of London.

prevent changes in respiration and circulation which may cause significant errors in the measurement. The inhalation must be made through the nose, with the mouth kept closed. In this way the mixture of air with the amyl nitrite vapor is less than it would be if the vapor were inhaled through the mouth. Consequently, before taking the measurement, it is necessary to make several tests of the patient's respiratory behavior. This is done by placing the unopened ampule directly under his nose and inviting him to take a deep and rapid breath, and then continue to breathe normally and quietly. Only after having made several trials, and being sure of the perfect collaboration of the patient, can the measurement be started. Attention must be drawn to the fact that the ampule explodes when opened. By this warning the perturbing effect can be lessened or avoided. Before the process is begun, the patient is informed that, several seconds after the first and only deep inhalation of amyl nitrite vapor, a definite sensation of heat will be felt in the face, together with a pounding of the pulses in the head and a certain feeling of heaviness and quickening of the heartbeat; these effects of the drug have no annoying intensity and will disappear within a few minutes. The patient is instructed to report immediately the first clearly felt sensation of heat in the face by uttering the word "Ya." That represents the end of the process. The measurement by chronometer begins with the first and only deep breath and ends with the first clearly felt heat in the face, indicated by the patient's saying "Ya." The chronometer is then stopped. It is not feasible to substitute observation of flushing of the face by the examiner for the subjective sensation of heat felt by the person under examination, because nervous excitement and emotion, by the psychomotor reflex mechanism, are able to produce similar flushes before the inhalation of the amyl nitrite, but with no definite feeling of heat. The other effects of inhalation of amyl nitrite vapor, such as cough, pounding of the pulse, and tears, are inconstant and not suitable for marking the end point of any measurement.

As a final observation about the technicalities of the measurement of the amyl nitrite circulation time (a.c.t.), the necessity of the patient's being recumbent during the test must be emphasized, in order to avoid incidents which may follow dizziness (faintness, even syncope).

RESULTS OF MEASUREMENTS IN 250 CASES

Normal Subjects (Table I).—In the group of one hundred normal persons, whose ages ranged from 16 to 70 years, with more than half between 30 and 50 years (58 cases), the amyl nitrite time varied between 14 and 25 seconds, with an average of 19.5 seconds, and the greatest number between 20 and 21

TABLE I. NORMAL SUBJECTS

A.C.T. (SEC.)	NUMBER OF CASES
14	7
15	8
16	7
17	6
18	7
19	9
20	14
21	12
22	9
23	9
24	7
25	5
Total	100
Average a.c.t. for normal subjects	19.5 sec.
Range	14 to 25 sec.

Relation of Age to A.C.T. in Normal Subjects

AGE (YRS.)	NUMBER OF CASES	AVERAGE A.C.T. (SEC.)
10 to 20	5	17.4
20 to 30	13	18.4
30 to 40	22	18.0
40 to 50	36	20.0
50 to 60	12	21.7
60 to 70	11	21.7
70 and over	1	24.0

seconds. The average amyl nitrite time in relation to each age group, classified with differences of ten years, enabled the recognition of the fact (previously established with different methods) that the velocity of the blood flow diminishes with increasing age. The average a.c.t. in the group of youngest persons was 17.4 seconds. In the groups of older persons the velocity showed a linear tendency to decrease, and a maximum of 24 seconds was recorded in the oldest group.

The intensity of the heat sensation was well marked in every case, and in the group of healthy persons it was possible to establish the fact that the intensity of the feeling of heat in the face was directly proportional to the velocity of the blood flow. A more intense sensation was felt in cases of higher velocity (shorter amyl nitrite time), and a milder one if the velocity of the blood was slower.

The most frequently observed (side action) was a slight degree of dizziness that disappeared completely in two to five minutes. Also, the frequent flushing of the face, with or without tears, induced in the patient a strange but not disagreeable feeling. The heart rate changes, as registered by the electrocardiograph and recorded simultaneously with the inhalation of the amyl nitrite vapor, were very different. In some cases the heart rate remained unchanged, but in the majority it increased forty to fifty pulsations per minute, then returned to the initial rate within one or two minutes. In the group of healthy persons the measurement was reliable in every case.

Decompensated Cardiac Patients (Table II).—The experience acquired in the examination of one hundred fifty patients with different degrees of heart failure reinforces the established correlation between the intensity of the warm sensation provoked by the inhalation of amyl nitrite vapor and the velocity of the blood flow. In general, the heat sensation in the faces of decompensated cardiac patients decreased with diminished blood velocity, and in advanced stages it was impossible to establish any reaction. Above an a.c.t. of 50 seconds, the warm sensation was very mild or practically imperceptible by the patient. The measured values of the a.c.t. of decompensated cardiac patients were larger than those of people in normal health, and a tendency existed, but not in a mathematical sense, to find a prolonged circulation time associated with cases of a more advanced degree of decompensation, judged by the sub-

TABLE II. DECOMPENSATED CARDIAC PATIENTS

NUM- BER	NAME	AGE (YRS.)	BLOOD PRESSURE (MM. HG.)	VITAL CAPACITY (C.C.)	DYSP- NEA	A.C.T. (SEC.)	CLINICAL DIAGNOSIS
1	M. S.	64	150/ 80	1,800	+++	54	Arteriosclerotic heart disease
2	F. M.	60	120/ 80	1,900	+++	47	Arteriosclerotic heart disease
3	J. U.	60	130/ 50	2,000	++	45	Aortic insufficiency
4	M. E.	46	120/100	1,800	+++	45	Mitral valvular lesion
5	F. U.	78	110/ 60	3,400	+++	45	Aortic insufficiency
6	J. U.	60	130/ 50		++	40	Aortic insufficiency
7	R. N.	73	90/ 50	1,600	+++	39	Arterial hypertension
8	M. C.	60	200/140	1,000	+++	35	Arterial hypertension
9	M. R.	38	120/ 80		+++	35	Mitral valvular disease
10	N. G.	70	140/ 90	2,400	++	34	Arteriosclerotic heart disease
11	M. G.	55	90/ 70	2,600	++	34	Chronic myocardial infarction
12	I. P.	58	90/ 60	2,500	++	34	Arteriosclerotic heart disease
13	H. L.	59	150/ 10	3,100	+	34	Arterial hypertension
14	J. M.	64	120/ 60	1,600	++	32	Cor pulmonale
15	R. L.	63	120/ 90	1,600	++	32	Arteriosclerotic heart disease
16	G. F.	60	120/ 80	2,400	+	32	Arteriosclerotic heart disease
17	D. R.	62	140/ 80	3,200	++	32	Arteriosclerotic heart disease
18	A. B.	51	100/ 60	2,800	+	32	Arteriosclerotic heart disease
19	K. K.	42	120/ 70	3,000	+	32	Chronic myocardial infarction
20	A. P.	56	120/ 80	2,100	++	31	Arteriosclerotic heart disease

jective symptoms of shortness of breath and the objective findings of pulmonary and hepatic congestions and edemas. According to the experience acquired by the systematic application of amyl nitrite for the measurement of circulation time, the vital capacity is the objective sign which is most intimately related to the velocity of the blood flow. Diminished vital capacity, with other characteristic respiratory factors of cardiac origins that indicate pulmonary congestion and more enlarged cross section of the pulmonary vascular tree, was constantly accompanied by prolonged amyl nitrite circulation time. This correlation appeared evident not only by the comparison of the absolute values of vital capacity in different individuals, but especially in the same person in different conditions of compensation.

Compensated Cardiac Patients (Table III).—These cardiac patients showed an a.c.t. which was quite normal or slightly prolonged, with a normal or slightly diminished warm sensation. Among the different objective signs of heart failure, the parallelism between vital capacity and amyl nitrite circulation time was remarkable.

TABLE III. COMPENSATED CARDIAC PATIENTS

NUM- BER	NAME	AGE (YRS.)	BLOOD PRESSURE (MM. HG)	VITAL CAPACITY (C.C.)	A.C.T. (SEC.)	CLINICAL DIAGNOSIS
1	E. B.	31	100/60	2,100	27	Mitral stenosis
2	E. G.	31	110/70	2,700	27	Mitral stenosis and insufficiency
3	J. A.	48	130/90	2,600	25	Chronic myocardial infarction
4	J. F.	45	90/70	2,700	24	Angina pectoris
5	F. J.	56	120/80	3,000	23	Angina pectoris
6	S. U.	49	110/70	3,000	21	Angina pectoris
7	V. C.	65	100/70	3,100	20	Angina pectoris
8	A. H.	48	120/70	4,300	20	Aortic insufficiency
9	G. L.	56	140/80	3,400	18	Arteriosclerotic heart disease
10	J. B.	61	110/70	4,200	17	Chronic myocardial infarction

To illustrate this parallelism between the velocity of blood flow measured by amyl nitrite and the clinical aspects during different conditions of the compensation, the following cases are quoted:

CASE 1.—R. R., aged 73 years, was 166 cm. in height, and weighed 71 kilograms. He consulted his physician because of shortness of breath, dyspnea on exertion, insomnia, and nocturnal attacks of paroxysmal dyspnea. Physical examination revealed a slight degree of cyanosis, conjunctival jaundice, jugular ingurgitation, edema of the lower extremities, moist râles at the bases of both lungs, diminished heart sounds, and existence of a gallop rhythm. The liver was palpable for 4 fingerbreadths below the costal arch. The blood pressure was 90/50. Roentgenologic examination showed enlarged hilar shadows, pulmonary areas with congestive aspects, intense diminution of the transparency, and a certain amount of hydrothorax on both sides. The heart was generally enlarged with a greater preponderance of the left ventricle; the long diameter measuring 15 centimeters. The movements of the heart shadow were diminished. The electrocardiogram showed sinus rhythm with a heart rate of 92 per minute and with electrical left axis deviation. P_1 was positive; P_2 was isoelectric; and P_3 was negative. R_2 was notched; T_1 was negative; T_2 was isoelectric; and T_3 was positive. The S-T junction in Leads I and II was below the reference level and, in Lead III, was slightly above. PQ measured 0.20 second and QRS 0.10 second.

Diagnosis: myocardial damage, both auricular and ventricular, and signs of intra-ventricular conduction trouble. In this condition the vital capacity measured 1,600 c.c. and the a.c.t. was 39 seconds. Treatment was initiated immediately with strophanthin combined with aminophylline intravenously every day, to which one ampule of Esidrone was added every five days. After twenty days of treatment the patient improved noticeably and a control examination revealed no signs of pulmonary congestion. The liver was smaller (its inferior border was palpable 2 fingerbreadths below the costal arch), and the

edema of the legs had disappeared. The blood pressure rose to 115/50; the pulse rate diminished to 72 per minute. The vital capacity increased to 2,500 c.c., and the amyl nitrite circulation time was reduced to 17 seconds.

In the next two weeks the patient, against medical advice, took no medicines, a mistake which rapidly resulted in a severe setback, and a clinical examination showed him to be in the same condition as he was before treatment began. The vital capacity was exactly the same, i.e., 1,600 c.c. and the a.c.t. of identical value, 39 seconds.

CASE 2.—E. C., 60 years of age, had hypertension and congestive heart failure. She was suffering from shortness of breath, dyspnea on exertion, and a cough for more than ten years. Examination revealed that the patient had slight cyanosis in the face and ingurgitated veins in the neck with irregular pulsations. There was very pronounced anasarca in the legs. The liver was palpable at the level of the navel, and ascites was present. Auscultation revealed rare moist râles at the bases of the lungs, and the heart sounds were accentuated with a systolic murmur at the apex. The roentgenologic examination showed clear pulmonary areas with slight hydrothorax in the left side. The heart shadow was extremely enlarged, especially the left ventricle which was in contact with the thoracic wall. The long diameter was 22 cm.; the arch of the right auricle was pronounced; the shadow of the aorta was slightly enlarged; and the descendent segment was visible in the intrathoracic trajectory. The electrocardiogram showed auricular fibrillation with a ventricular rate of 100 per minute. There was a left axis deviation. R_1 was the predominant wave of the ventricular complex in the first lead and S_3 in the third lead; both were notched. T_1 and T_2 were negative, and T_3 was positive. The S-T junction was deeply depressed below the isoelectric line in the first, and above it in the third, lead. QRS measured 0.12 second.

Diagnosis: auricular fibrillation, left bundle branch block, and myocardial damage. The blood pressure was 180/120. The a.c.t. result in this condition was 32 seconds.

In the following twenty days treatment was begun with venesection, 600 c.c., strophanthin with aminophylline intravenously in combination with salyrgan every four days. The patient was feeling much better and the objective signs of the decompensation were reduced. In this improved condition of compensation the circulation accelerated and measured 23 seconds by amyl nitrite. During the next month the strophanthin was replaced by digital but with no satisfactory results, and the patient returned with marked dyspnea and periodic breathing; the edemas also reappeared. The result of the measurement of the circulation time, in the patient's impaired condition, was 35 seconds.

In this observation the a.c.t. was a true indicator of the altered condition of the circulation and showed parallelism with the clinical aspect.

CASE 3.—E. G., 50 years of age, weighed 74 kg. and was 172 cm. in height. Eight years previously he had suffered from an attack of rheumatic fever and since then had begun to notice shortness of breath and pain in the chest without irradiation. The physical examination disclosed a pale patient with visible arterial pulsation in the neck. The liver was palpable 2 fingerbreadths below the right costal margin. The apex impulse was palpable in the sixth intercostal space in the anterior axillary line. Moist râles were heard at the bases of the lungs posteriorly. Over the aortic focus an intense sistolic diastolic murmur was heard, which was transmitted to the large vessels. The roentgenologic examination showed an enlarged heart shadow in "aortic configuration," and the heart measured 18.7 cm. in length. The electrocardiogram showed sinus rhythm with a heart rate of 96 per minute. Left axis preponderance was present, S_2 biphasic, T_1 and T_2 negative, and T_3 isoelectric. The S-T segment was displaced to below the isoelectric level. Arterial pressure was 120/60, vital capacity, 1,600 c.c., and the a.c.t., 28.5 seconds. Treatment was begun with digitalis, and the patient improved after twenty days, when the a.c.t. reached 24 seconds. Three months later the patient's condition was improved further still, and the vital capacity was 2,200 c.c. and the a.c.t., 20 seconds.

In this case the clinical improvement and the changes in vital capacity and circulation time clearly demonstrate parallelism.

CASE 4.—M. G., aged 60 years. Clinical diagnosis: chronic myocardial infarction and cardiac insufficiency. Three years previously he had suffered coronary thrombosis, and, since then, he had noticed shortness of breath, which had become more intense. Physical examination showed congestion of the lungs and diminished heart sounds. There was a loud systolic murmur heard over the apex area. The inferior edge of the liver was pal-

pable 3 fingerbreadths below the right costal margin. Roentgenologic examination detected a generally enlarged heart shadow with a preponderance of the left ventricle and a longitudinal diameter of 18.5 centimeters. The electrocardiogram showed sinus rhythm with a heart rate of 75 per minute. Electrical axis deviation was absent. Q_2 and Q_3 , were deep with notching; T_1 and T_2 , were isoelectric; and T_3 , was negative. In the precordial Lead CF_4 , a small R wave was present, not larger than 1 millimeter. T was positive and the S-T junction was elevated above the zero line. PQ measured 0.20 second and QRS, 0.10 second. The electrocardiographic signs described indicate myocardial damage as in cases of chronic myocardial infarction of the anterior wall of the left ventricle. The measured vital capacity was 2,600 c.c., and the a.c.t. was 34 seconds. After being treated for a month with strophanthin and deriphyllin intravenously, the patient was noticeably improved. A repetition of the same examination resulted in 3,000 c.c. for the vital capacity and 29 seconds for the amyl nitrite time—an improvement in both factors.

CASE 5.—J. V., 49 years of age, had rheumatic heart disease with mitral stenosis and cardiac insufficiency. His chief complaints were shortness of breath, palpitation, and swelling of the abdomen. Râles were present in both lung bases; the heart rhythm was totally irregular, rate, 100. There was an accentuation of the first sound over the apex and a diastolic murmur. The second sound was accentuated over the pulmonary area. The roentgenologic examination detected a cardiac enlargement in all diameters with mitralization and an enlargement of the pulmonary vessels with diminished transparency of the pulmonary areas. The electrocardiogram showed auricular fibrillation, no electrical axis deviation, an isoelectric T_1 , a flattened T_2 , and a positive T_3 . In the precordial Lead CF_4 , there was a profound displacement of the S-T intervals below the isoelectric line. The blood pressure was 90/60; the vital capacity was 2,500 c.c.; and the circulation time, measured by amyl nitrite, was 30 seconds. The treatment employed consisted in taking digital in intermittent form combined with one injection of salyrgan weekly, which brought the patient to a satisfactorily improved condition, and, four months later, the tests taken showed a vital capacity of 3,000 c.c. and an a.c.t. of 19 seconds.

CASE 6.—K. K., aged 45 years, weighed 89 kg. and was 191 cm. in height. He had arterial hypertension and complained of high blood pressure, nervousness, and slight shortness of breath on exertion. The clinical examination revealed a normal lung condition, and the heart sounds were clear and of normal intensity. Roentgenologic examination showed enlargement of the heart shadow to the left with a longitudinal diameter of 16.5 centimeters. The electrocardiogram showed a sinus rhythm of 60 contractions per minute with pronounced left axis deviation. T_1 was negative; T_2 and T_3 were positive; and the S- T_1 interval was deeply displaced below the isoelectric line. The auriculoventricular conduction time was 0.20 second, and QRS was 0.10 second. These electrocardiographic findings were as usual in cases of marked hypertrophy of the left ventricle as in hypertensive heart disease. The arterial blood pressure was 170/120, the vital capacity, 4,000 c.c., and the a.c.t., 37 seconds. The treatment prescribed consisted of small doses of digital continuously, combined with tablets of aminophylline and phenobarbital. The patient came back after three months, reported improvement, and examination at that time revealed an arterial pressure of 150/110, a vital capacity of 4,500 c.c., and an a.c.t. of 29 seconds.

In all these observations, according to the clinical improvement, the objective signs of a better circulation as well as the vital capacity and the amyl nitrite circulation time showed parallelism, i.e., values nearer to normal.

Acceleration of the Circulation (Table IV).—In this small group of patients who clinically showed multiple evidence of hyperthyroidism the a.c.t. was definitely shortened, rising to 8 seconds, which is equal to one-third of the normal value, i.e., there exists a strongly accelerated circulation. In these cases the intensity of the heat sensation in the face was very sharp. There was burning, intense flushing, pronounced tears, violent palpitation—not only in consequence of hemodynamic causes (greater concentration of amyl nitrite vapors in the peripheral blood following a more rapid transportation by the accelerated circulation)—but because, in this condition, a greater nervous excitability exists. However, this undesirable side action of amyl nitrite, apart from the nervous impression, causes no serious trouble. In regard to the correlation of the velocity

TABLE IV. ACCELERATION OF THE CIRCULATION

NUM- BER	NAME	AGE (YRS.)	BLOOD PRESSURE (MM. HG)	VITAL CAPACITY (C.C.)	A.C.T. (SEC.)	CLINICAL DIAGNOSIS
1	G. A.	34	150/90	3,200	8	Hyperthyroidism
2	N. B.	27	140/60	3,600	10	Hyperthyroidism
3	A. G.	30	100/70	3,000	11	Hyperthyroidism
4	J. O.	33	90/50	3,500	12	Hyperthyroidism
5	G. B.	44	100/70	3,800	13	Hyperthyroidism

of the blood flow to the vital capacity, the observation can be made, that notwithstanding the fact that the vital capacity shows normal values, the cyphers that were found represented the minimal variation within the proportional. There are certain divergences between the relative high speed of the blood flow and the relative low amount of air expressed by the vital capacity.

Pulmonary Emphysema (Table V).—In this characteristic group of patients who complained principally of shortness of breath and dyspnea on exertion, and in whom the clinical examination revealed no evidence of cardiac disease, or only in such a slight degree that it did not elucidate their intensive reduction of the functional capacity, and who generally showed a significantly diminished vital capacity, the amyl nitrite circulation time was perfectly normal or slightly prolonged. Although the amyl nitrite vapors inhaled were only a fraction of the amount normally introduced, as a result of the reduced respiratory air volumes, the intensity of the warm sensation in the face was perfectly normal in these cases of pulmonary emphysema. Among them it is impossible to recognize a parallelism between the vital capacity and the circulation time because very different values of vital capacity can be associated with an identical value of blood velocity. The experiments made by measurement with amyl nitrite affirm the integrity of the circulation in cases of bronchial asthma or emphysema where the cause of the shortness of breath is due to pulmonary (respiratory) factors and not to circulatory failure. Of course, if the emphysema is of long duration, or if it comprises the heart, the amyl nitrite time will be prolonged as in any other case of heart failure.

The normal intensity of the warm sensation in emphysematous patients demonstrates that the amount of amyl nitrite vapors inhaled in one breath is sufficient for its production, and a greater quantity does not provoke a shortening of the amyl nitrite circulation time.

TABLE V. PULMONARY PATIENTS

NUM- BER	NAME	AGE (YRS.)	BLOOD PRESSURE (MM. HG)	VITAL CAPACITY (C.C.)	A.C.T. (SEC.)	CLINICAL DIAGNOSIS
1	I. D.	57	160/ 90	1,000	22	Bronchial asthma, emphysema
2	A. P.	62	110/ 80	1,000	25	Emphysema
3	A. K.	60	130/100	1,100	26	Emphysema
4	C. B.	54	120/ 70	1,200	22	Bronchiectasis, emphysema
5	E. D.	28	130/ 90	2,100	15	Bronchial asthma
6	E. Q.	46	120/ 80	2,200	22	Emphysema
7	E. S.	54	120/ 70	2,200	19	Tuberculosis, chronic fibrosis
8	F. V.	70	140/ 90	2,200	27	Chronic bronchiectasis, emphysema
9	F. S.	68	130/ 90	2,200	23	Emphysema
10	J. S.	55	140/100	2,300	21	Emphysema

Duplicate Measurement (Table VI).—In several cases duplicate measurements were taken. A second test was made ten minutes after the first one, without any noticeable discomfort to the patient. The results of the second measurement were identical with the first in the majority of cases, or differences were

TABLE VI. DUPLICATE MEASUREMENTS

NUMBER	FIRST MEASUREMENT (SEC.)	SECOND MEASUREMENT (SEC.)	DIFFERENCE (SEC.)	CLINICAL DIAGNOSIS
1	29	29	0	Arteriosclerotic heart disease
2	22	22	0	Normal
3	19	21	2	Thyrotoxic heart disease
4	45	47	2	Arteriosclerotic heart disease
5	32	35	3	Arteriosclerotic heart disease
6	24	27	3	Arteriosclerotic heart disease
7	24	28	4	Arteriosclerotic heart disease
8	39	34	5	Arterial hypertension
9	24	19	5	Normal
10	17	25	8	Normal

registered of between two to five seconds only. In some rare instances the differences were larger. This inconstancy of amyl nitrite measurement (which has also been observed in other methods such as Lilienfeld and Berliner³) is a peculiarity not yet explained, neither by the methods nor by the circulation itself.

Comparative Measurement With Other Methods (Table VII).—In a small group of ten healthy persons simultaneous measurements were made of the arm-to-tongue time by calcium bromide⁸ (1 c.c. of 50 per cent Br. 2 Ca.), the arm-to-lung time by ether, and the lung-to-face time by amyl nitrite. The results of these simultaneous measurements by different methods gave concordant values, i.e., normal for each system of determination, but it was not possible to find numerical equivalents between the different methods employed. The calculated value of lung-to-face time, i.e., the indirect determination of the functional capacity of the left ventricle will be obtained by subtracting the ether time from the total circulation time (the calcium bromide time), the remainder being the lung-to-face time. In each case observed, the number of amyl nitrite seconds equivalent to the corresponding number of calcium seconds was always different. However, the same criticism may be justly applied, in general, to all systems of measuring circulation time, because it is erroneous to consider as equal one second of ether time and one second of calcium, decholin, histamine, or amyl nitrite time.

TABLE VII. COMPARATIVE MEASUREMENT OF THE VELOCITY OF BLOOD FLOW IN NORMAL PERSONS

NUMBER	NAME	AGE (YRS.)	AMYL NITRITE (SEC.)	CALCIUM BROMIDE (SEC.)	ETHER (SEC.)
1	G. C.	16	24	13	7
2	M. A.	45	22	12	7
3	H. A.	22	22	12	7
4	Z. C.	30	20	12	8
5	F. O.	29	21	13	7
6	D. C.	42	21	17	6
7	C. P.	30	20	14	8
8	G. P.	46	20	13	7
9	F. S.	29	18	15	8
10	E. C.	16	16	10	8

Impracticable Measurement.—In the series of one hundred fifty cardiac patients the measuring of the circulation time by amyl nitrite failed in seven cases. Five of these were cardiac patients in a condition of severe decompensation with intense pulmonary engorgement and edemas. Either the heat sensation in the face was very feeble so that the patient hardly felt it, or it was simply absent. A repetition of the measurement on the same day gave an identical

result. After commencing adequate treatment, new measurements were taken when the conditions had improved and showed, according to the degrees of decompensation, a prolonged but definite circulation time. The other two patients were individuals who betrayed slight mental symptoms, such as depression, because of intense edema and slight uremic retention, respectively. In these cases satisfactory mental collaboration was not obtained.

Incidents.—In the case of a patient suffering from acute glomerulonephritis with a blood pressure of 200/120, a very intense headache appeared after he had inhaled the amyl nitrite vapors and marked a circulation time of 26 seconds. The headache lasted for ten minutes and passed away without any consequences. This headache also appeared in other cases of hypertension, but in a milder degree. Consequently, in order to avoid this inconvenience, measurement has been omitted in cases where the blood pressure is higher than 200.

DISCUSSION

Amyl nitrite, introduced into therapeutics by Brunton,⁹ in 1867, has been studied intensely in order to explain the mechanism of its action. According to the actual stage of our knowledge, the vasodilation produced by the inhaling of its very volatile vapors is caused by its direct action on the unstriated muscle of the peripheral vessels, both arteries and veins. Cushny¹⁰ pointed out that the peripheral effect of the amyl nitrite can easily be demonstrated by experiments made on the amputated legs of animals—the amount of perfusion liquid that was leaving the vein rose immediately if some drops of this substance were introduced with the liquid of perfusion into the artery of the amputated leg. The appearance of flushing and heat in the face indicates the arrival of the blood containing amyl nitrite at the vascular territory of the face and thus represents the end point of the measure. The run of the amyl nitrite inhaled begins with the respiratory tract, from the trachea to the alveoli, where it reaches the extensive capillary bed of the lungs and is absorbed. From the pulmonary capillaries the veins of the lungs carry it to the left heart and from here it is taken to the arterial circulation.

Evidently the expression amyl nitrite circulation time does not mean exclusively the objective time duration of the blood movement from the initial point to the end of the trajectory, but it represents the sum of different sub-times, among which the most important are (1) the duration of one deep inspiration, (2) the velocity of absorption through the alveolar membrane, (3) the time required for the transfer of the blood from the pulmonary capillary area to the vascular bed of the face, (4) the time required to produce the warm sensation, (5) the time of the psychomotor reaction of the patient, indicating the presence of the warm sensation, and (6) the time of the psychomotor reaction of the observer who is recording the circulation time.

The decisive factor in determining the numerical value of the circulation time is, without doubt, the real circulation time, i.e., the duration of the circulatory movement of the blood from the initial point to the end point of the trajectory, while all the other factors mentioned are of secondary importance. The duration of a deep breath, determined in many cases, ranged between 1 and 1.5 seconds following the introduction of the amyl nitrite vapors into the circulation by a deep breath required identical times as the intravenous injection of 1 or 2 c.c. of an aqueous solution employed for the measurement of the circulation time. The condition of the nervous state, especially the clear sensorium, whose influence we cannot appreciate quantitatively, must, nevertheless, be attended to.

The amyl nitrite circulation time must be considered as the average value of the *fastest* transport of blood from the pulmonary capillaries to the minute vessels of the face. It is a peculiarity of the amyl nitrite measurement that the amount of vapors inhaled is not exactly dosed, but experience demonstrates that the amount of amyl nitrite vapors inhaled by a deep breath is more than sufficient to provoke a definite sensation of warmth in the face, because, in conditions of bronchial asthma or emphysema, the amount of air inspired is only a third or a fourth of the normal, yet the appearance of the heat sensation occurred in times and intensity considered as normal, too. A larger amount of amyl nitrite by forced deep inspiration did not shorten the appearance of the warm sensation, but it did reinforce its intensity. According to all these considerations, the most rapid and the most intense warm sensation will be observed in hyperthyroidism, where the effective rapid blood velocity allows the arrival of amyl nitrite, inhaled in normal amounts, in higher concentrations in the periphery and to all these hemodynamic reasons must be added the increased nervous sensitivity, characteristic of this condition, that reinforces the intensity of the warm sensation. The inverse takes place in heart failure. The amount of inspired amyl nitrite is diminished following the decreased respiratory volume, the velocity of the blood flow is less, and the concentration of amyl nitrite in the blood is lower, not only as a consequence of the slower circulation, but also on account of the higher degree of dilution determined by the increased amount of blood contained in the enlarged cross section of the pulmonary vascular bed.

The close relation existing between the a.c.t. and the vital capacity indicates the importance of the state of the pulmonary circulation, the degree of opening, and blood repletion to the velocity of blood flow. The experiences with measurements of amyl nitrite indicate the tendency of a parallelism in different persons showing fastest circulation in cases of increased values of vital capacity, while the repeated measurements in the same individuals during treatment of decompensation corroborate the same observation. The changes of the width of the cross section of the pulmonary vascular tree and the changes of their blood content unquestionably are the most important factors for the delay of circulation in regard to the trajectory measured by amyl nitrite. The suggestions of Nylin¹¹ about the importance of intracardial residual blood as a retarding factor for the circulation has been studied in the present work. The heart volume was estimated radiologically by the Rohrer-Kahlstorf¹² method, without possibilities of establishing correlation in a definite sense between cardiac volume and circulation time because the heart volumes were greatly enlarged (f.i. 1,250 c.c. or more) with normal shortened circulation time (17 seconds [a.c.t.]). But it seems without question that this new point of view of the intracardiac congestion with the resulting increased volume of residual blood represents another possibility for hemodynamic interpretation of prolonged circulation time.

The circulatory trajectory measured by amyl nitrite corresponds properly to the left ventricle. However, based on the results of amyl nitrite measurement, an accurate differentiation between left or right ventricular failure is impossible, because the same values of circulation times can be observed in both cases. The multiple biologic compensations between the hemodynamic factors of the circulation can neutralize partial effects, thus compensational adaptive changes of systolic output, circulatory blood volume, cross section of the vascular bed, and even functional short circuits can determine great individual variability in the resulting value of circulatory velocity. In cases of slight decompensation, precisely within the compensatory capacity of the

circulation, the a.c.t. can remain perfectly normal or scarcely prolonged and only if the degree of heart failure overwhelms the compensation capacity of the circulation will it be prolonged. As a matter of fact, in the clinical picture there was no parallelism between the intensity of subjective discomfort, especially shortness of breath, and prolongation of a.c.t., but it is true that in advanced cases of decompensation the a.c.t. never was normal and in normal conditions of the circulation the amyl nitrite measurement never was prolonged. For all these reasons, as much theoretical as practical, the value of the measurement of the circulation time must be interpreted individually.

SUMMARY

1. A new method for the measurement of the lung-to-face circulation time, using amyl nitrite as an agent, is outlined. The technique of administration is described, and normal values and their correlations are established. The method is simple, needs no apparatus nor assistants, and can be performed by the examiner alone.

2. The amyl nitrite circulation time (a.c.t.) measures the functional capacity of the left ventricle and is determined essentially by the condition of the pulmonary circulation recognizable by the vital capacity. There exists a tendency of parallelism as much in the absolute value of both factors as especially in their modifications in different conditions of compensation in the same person.

3. The inverse correlation is established between the a.c.t. and the intensity of the warm sensation: more intense heat with shortened circulation time and vice versa.

4. In conditions of heart failure, the a.c.t. is prolonged, and the intensity of the warm sensation is diminished, but there is no strict parallelism with the clinical features.

5. In hyperthyroidism the a.c.t. is shortened and the intensity of the warm sensation is strongly reinforced. Emphysema or bronchial asthma, not complicated by heart failure, are characterized by normal a.c.t. and normal intensity of the warm sensation.

6. Subminimal a.c.t., except for existing intracardial or arteriovenous short circuits, never is observed *with* cardiac failure; largely prolonged a.c.t. never is observed *without* heart failure. Medium values of a.c.t. are as compatible in persons of normal circulation as in those with slight failures of it.

7. A differentiation between left or right ventricular failure is not possible, based upon the amyl nitrite measurement.

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COARCTATION OF THE AORTA

REPORT OF TWO CASES, RELATING CLINICAL DATA TO DEGREE OF CONSTRICTION MEASURED AT AUTOPSY, WITH A METHOD OF STANDARDIZATION FOR RELATED MEASUREMENTS

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THE following two cases illustrate the difficulty sometimes encountered in the diagnosis of aortic coarctation. Both represent modes of death that are not common in this disease.

CASE REPORTS

CASE 1.—This 20-year-old white man is known to have been rejected by the Armed Forces in February, 1943, because of hypertension (systolic blood pressure about 180). Several months before death he was examined at this clinic because of abdominal pain, nausea, and vomiting. At that time his blood pressure was 160, systolic, and 70, diastolic. Four weeks before death, in January, 1944, he was admitted with complaints of frontal headaches, facial edema, and dimness of vision. He told about an episode of chills and fever followed by joint pains, occurring late in 1943, and recurring about one month later, accompanied by hematuria and nocturia. At that time he noted small, painful, red nodules on his legs.

Physical Examination.—The patient was a pale, undernourished young adult with moderate, generalized edema. On his breath was a uriferous odor. The left border of the heart extended 11.5 cm. to the left of the midsternal line in the fifth intercostal space. A blowing systolic murmur was heard best in the mitral area. The second aortic sound was louder than the second pulmonic sound. The liver was palpable 3 fingerbreadths below the costal margin.

The blood pressure was taken in all extremities. It was 30 degrees higher, systolic, and 5 to 15 degrees higher, diastolic, in the arms than in the legs. Throughout his illness the right brachial pressure averaged 180, systolic, and 90, diastolic. Comparison of brachial and crural pulses was not made.

Pertinent laboratory data appear in Table I. The patient was treated for his obvious kidney ailment, to which his hypertension was thought to be related. For most of his course, his temperature was subnormal; it was definitely not septic. No blood cultures were taken. The highest temperature reading was 38.5° C. He died on the twenty-fourth hospital day in circulatory failure and uremia.

Autopsy (Duke 3981).—The heart weighed 470 grams. The dilated left ventricle was 2 cm. thick. On both sides of the interventricular septum was a dense, white endocardial thickening, closely related to the septum fibrosum, suggesting late closure of a ventricular septal defect. The aortic valve was bicuspid. No other intracardiac anomalies were present. The measurements of significance regarding the heart and aorta are given in Table II.

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TABLE I. LABORATORY DATA

DATE AD- MITTED	B.P.	ECG	HGB.	R.B.C.	W.B.C.	SED. RATE	N.P.N.	MICR. URINE*	BL. CUL.†	WT. (LB.)
<i>Case I</i>										
Jan. 1944	180/90	Slight left axis devia- tion	6.5	61 M	10,800	15	153- 210	2 to 3 W.B.C./ HPF‡ 5 to 20 R.B.C./ HPF	None	—
<i>Case II</i>										
Sept. 1943	140/80	Slight left axis devia- tion	10.4	3.43 M	4,160	26	28	Neg.	Alpha Strep- tococci (3x)	133
Oct. 1943	150/70	Slight left axis devia- tion	11	3.73 M	7,240	0	30	1 to 4 W.B.C./ HPF	Alpha Strep- tococci (3x)	125
Feb. 1944	130/70	Slight left axis devia- tion	6.1	1.63 M	5,200	14	24	5 to 20 W.B.C./ HPF 10 to 25 R.B.C./ HPF	Alpha Strep- tococci (3x)	121

*Microscopic study of urine.

†Blood culture.

‡High-power field.

The great branches of the aortic arch were situated in normal relation to one another. The ostium of the left subclavian artery was considerably enlarged. Two centimeters below this, just at the level of the aortic end of the ligamentum arteriosum, there was a 2 mm. thick diaphragm with a central opening having a circumference of 1.5 centimeters. The right half of the aorta, distal to the coarctation, was covered with large, friable vegetations. These proved to be attached to thrombotic material within an aneurysm 4 by 3 cm. in diameter. The second right intercostal artery was found on the inferior wall of the aneurysm, but the first right intercostal artery was lost in the aneurysmal formation. Cultures from purulent material in the aneurysm grew alpha streptococci. The outer limit of the aneurysm was formed by the esophageal wall, considerable destruction of which was evident grossly and microscopically. The iliac arteries were not dilated.

No other bacterial aneurysms were encountered. Clear fluid was found in all serous cavities (2,000 c.c. in the abdomen). Old and new infarcts marked the soft, flabby spleen (weight, 250 grams) and the gray-yellow kidneys. The latter were speckled with hemorrhages and, microscopically, showed a marked degree of damage from subacute diffuse and embolic glomerulonephritis.

TABLE II. STANDARDIZED MEASUREMENTS

	NUMBER MEAS- URED	MEAN (CM.)	STAND- ARD DE- VIATION	STAND- ARD ERROR	CASE I (CM.)	CASE II (CM.)
Left ventricular wall	9	1.53	.260	.062	2.0	2.0
Aortic ring, circumference	8	6.35	.247	.064	6.0	6.0
Aorta 2 cm. from base	9	5.82	.598	.143	5.0	6.0
Innominate ostium	9	2.87	.558	.133	2.8	3.8
Subclavian ostium	9	2.03	.297	.071	3.5	1.5
Aortic circumference at subclavian artery	10	4.38	.299	.068	3.5	2.5
Coarctation circumference	—	—	—	—	1.5	2.0
Aorta at fourth intercostal artery	10	4.21	.227	.052	5.0	4.0
Aorta at seventh intercostal artery	10	3.97	.224	.051	3.4	3.5
Aorta at eleventh intercostal artery	10	3.60	.279	.063	2.8	3.6
Aorta at bifurcation	8	2.90	.471	.119	2.1	3.0

Anatomic Diagnosis.—Coarctation of aorta, adult types; bicuspid aortic valve; hypoplasia of abdominal aorta; cardiac hypertrophy and dilatation; chronic passive congestion of lungs; pulmonary edema; bilateral hydrothorax and ascites; chronic passive congestion of liver. Bacterial endocarditis (alpha streptococcus) with local extension through aortic wall into esophagus, mediastinal abscess, and acute mediastinal lymphadenitis; acute splenic tumor; bacteremia (alpha streptococcus); splenic and renal infarcts; subacute diffuse glomerulonephritis.



Fig. 1.

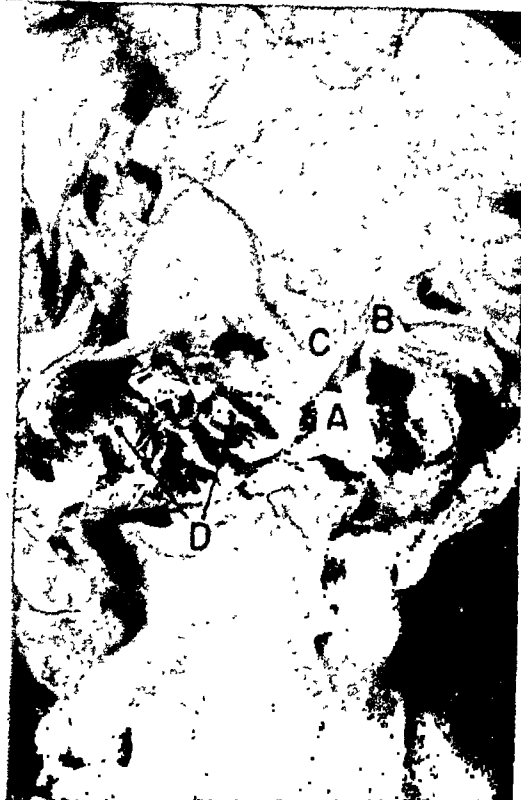


Fig. 2.

Fig. 1.—Case 1. The aorta is opened from the back to show the coarctation (A) at the level of the aortic end of the narrow ligamentum arteriosum (C). The aortic bacterial aneurysm (D) is below the coarctation, at the left side in the photograph. Its relation to the esophagus (E) is shown. The dilated ostium of the subclavian artery (B) is 2 cm. above the diaphragm of the coarctation.

Fig. 2.—Case 2. The aorta is opened from behind to show the constricting band (A) of the coarctation running from the caudal edge of the stenosed subclavian ostium (B) to the aortic end of the broad ligamentum arteriosum (C). The aortic bacterial aneurysm (D) is below the coarctation, at the left side in the photograph.

CASE 2.—A 22-year-old white man was observed over a six-month period. During this time blood stream alpha streptococci were repeatedly grown. At the age of 6 years the diagnosis of weak heart had been made and limitation of activity imposed because of precordial pain and dyspnea on exertion. Two brothers and four sisters and both parents were entirely free of cardiovascular complaints. The patient was accepted for Army service in 1940. In the winter of that year, during a period when his infantry company was housed in tents (North Carolina), this man suffered four or five episodes of dull precordial pain and swollen, painful joints. These episodes lasted seven to ten days. Transfer to Panama alleviated his suffering with the result that final discharge from the Army was postponed until 1941, following an exacerbation of symptoms. He suffered six additional episodes before his first admission to Duke Hospital in September, 1943. For three months he had been uncomfortable with diurnal, afternoon fever. His temperature was 39° C.

Alpha streptococci were grown from his blood, and he was treated with sulfamerazine combined with fever therapy. This therapy produced only temporary sterility of the blood as judged by repeated cultures. In mid-October he was discharged. Twenty days later he reappeared complaining of sudden mid-epigastric pain which had persisted for five days as a dull ache. A sudden bout of right, lower quadrant pain, with rebound tenderness and a rise of 6,000 in his leucocyte count within twenty-four hours, led to exploratory celiotomy and removal of a normal, retrocecal appendix. The surgeon's note read: "There was no

evidence in the mesentery of the bowel of any thrombosis. Thorough search had been made." Several weeks postoperatively he was discharged, unimproved, but no longer suffering any severe local symptoms.

In February, 1944, ten days before death, he returned, complaining of precordial and epigastric pain, swollen legs, and puffy face. Sudden, sharp, knifelike, precordial pain had occurred in January, persisting as a dull ache with remissions and exacerbations. Occasional sharp pains in the pit of the stomach had troubled him. Joint pains recurred in early February and were accompanied by peripheral edema, an entirely new symptom.

Physical Examination.—The patient was an obviously ill, emaciated young adult with slight cyanosis, marked pallor, and facial edema but no petechiae. The lungs were clear. The heart was moderately enlarged to the left. No thrills were palpable. A loud systolic murmur was audible over the entire precordium, maximally at the left sternal border, particularly in the pulmonic area. The second aortic sound was louder than the second pulmonic. The tense abdomen was ubiquitously tender, and the liver edge was palpable just at the costal margin. The spleen and kidneys were not palpable. The right knee and ankle were tender on palpation and on voluntary motion. There was slight edema of the lower extremities.

The blood pressure was not taken in the lower extremities at any time during the patient's three admissions. There was never any comparison of brachial and crural pulses. Table I records the blood pressure (right arm) and pertinent laboratory findings for the three admissions. The temperature ranged daily from a low 37° C. at 8 A.M. to 39° C. at 4 P.M. during the first two admissions, but it never rose above 37.8° C. during the last admission.

The spleen became palpable several days before death. Twenty-four hours before death persistent nausea and vomiting began. Complaints of chest and abdominal pain continued. Four hours before death the patient sat bolt upright, screaming that he was blind. After thrashing around for a while, he became quiet and was found to be in shock. In response to treatment for shock, he rallied temporarily and evidence was obtained that he was not blind. Hemoglobin on the previous day had been 13.5 Gm.; now it was 4.5 Gm. He complained of abdominal pain; the abdominal wall was boardlike. His blood pressure, which had risen to 100, systolic, and 70, diastolic, soon fell again to an imperceptible level, and the patient expired.

Autopsy (Duke 4008).—The well-formed, undiseased heart weighed 380 grams. The foramen ovale was probe patent. The pulmonic end of the ductus arteriosus admitted a blunt probe for a distance of 1 mm.; the aortic end, 4 millimeters. The total length of this obliterated artery is 14 millimeters. Nowhere in the heart was there evidence of endocarditis or rheumatism. Measurements of significance regarding the heart and aorta are given in Table II. The branches of the aortic arch were situated in normal relation to one another. The aorta became abruptly narrowed in a funnel-like manner at the level of the left subclavian. From the stenosed ostium of the left subclavian, an intimal elevation or constricting band ran to the obliterated ductus arteriosus. The band occurred on the convex curvature of the arch, producing an externally perceptible indentation. The ostium of the subclavian was just proximal to one end of the band; the aortic ostium of the ductus arteriosus was just distal to the other end. Delicate vegetations were seen both on the caudal edge of the constriction band and in a number of places on the multilobular aneurysm which occurred on the right, posterior aspect of the aorta immediately below the ductus. The orifices of the right first to third and the left first intercostal arteries were involved in the aneurysm. The mouth of the 3 cm. deep aneurysm was 3 cm. in diameter. Several soft lymph nodes, about 1 to 2 cm. in diameter, and areolar tissue in the region of the tracheal carina were adherent to the outer wall of the aneurysm. Pus, a smear from which showed gram-positive cocci in chains, occurred in abscesses found between the aneurysm and the enlarged lymph nodes.

Other bacterial aneurysms were encountered in dissection of the abdomen. Three thousand cubic centimeters of partially clotted blood were found in the peritoneal cavity. The site of hemorrhage was a ruptured aneurysm of the superior mesenteric artery, 5 cm. from its origin. The intramesenteric hemorrhage from this saccular aneurysm, 2.5 cm. in diameter, consisted of a kidney-sized mass of clotted blood. An almond-shaped rupture of the parietal peritoneum, 5 by 3 cm. in size, at the root of the mesentery, accounted for the intraperitoneal hemorrhage from the same source. An aneurysm 4 cm. in diameter, with considerable laminated, organized thrombus, found near the head of the pancreas, was in the celiac axis (Fig. 3). Halfway between the head and tail of the pancreas, in the splenic artery, was an aneurysm, 1.5 cm. in diameter, filled with fresh thrombus. Six similar aneurysms were found in the intrahepatic ramifications of the hepatic artery. The iliac arteries were not dilated.

Old and new infarcts were found in the soft, flabby spleen (weight, 300 grams) and in the kidneys. The left kidney weighed 210 grams and had a double pelvis and two ureters (with separate orifices in the bladder). An accessory renal artery, originating two segments below the usual one, entered the left kidney at the lower pelvis. The right kidney weighed 150 grams. Both kidneys present the typical appearance of diffuse embolic glomerulonephritis.

Anatomic Diagnosis.—Coarctation of aorta, adult type; probe-patent foramen ovale. Aortic endarteritis (alpha streptococci) with aneurysm formation, involving right first to third and left first intercostal arteries; bacterial aneurysm of celiac axis, splenic, superior mesenteric, and intrahepatic portions of hepatic arteries. Rupture of aneurysm of superior mesenteric artery with retroperitoneal hemorrhage and secondary rupture of posterior parietal peritoneum into abdominal cavity; hemoperitoneum (3,000 c.c.). Embolic glomerulonephritis (alpha streptococci); acute splenic tumor; splenic and renal infarcts. Cardiac hypertrophy, left sided (380 grams); complete double pelvis and ureters and accessory renal artery, left.

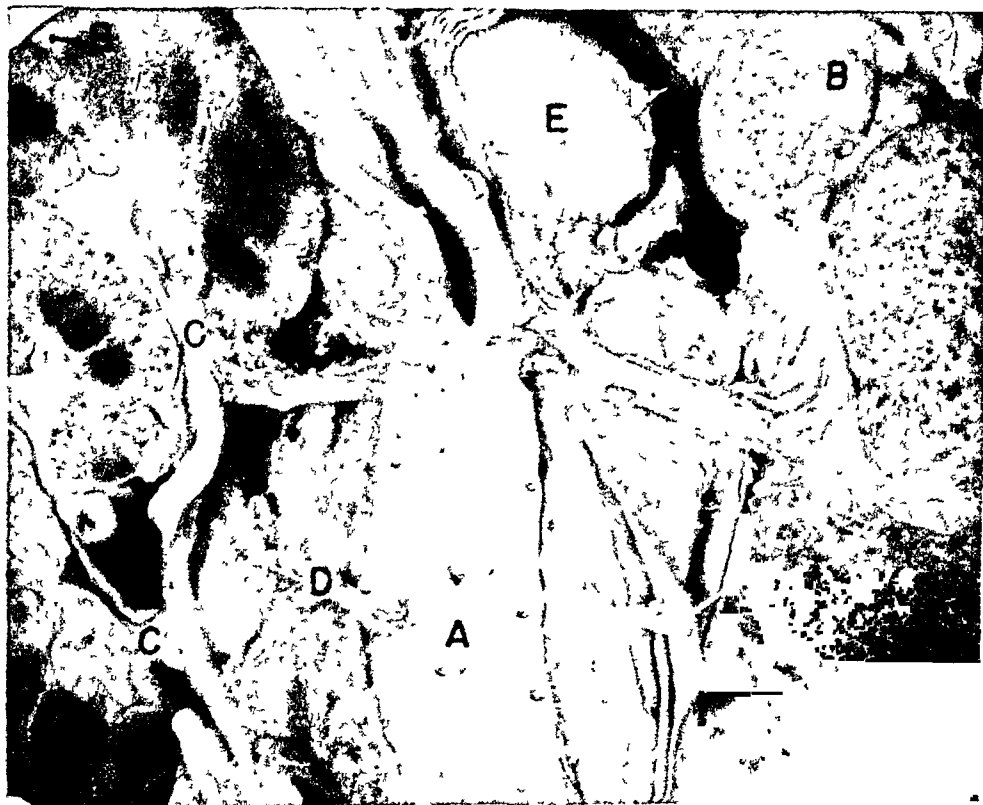


Fig. 3.—Case 2. The aorta (A) is opened from behind. The outer surface of the cortex (with capsule removed) of the right kidney is shown on the right and the cut surface of the left kidney, on the left. Diffuse punctate hemorrhages are seen in both kidneys. Fresh and old (scars) infarcts (B) are visible. The double pelvis and ureters (C) and accessory artery (D) of the left kidney are illustrated. Between the upper pole of the right kidney and the aorta is an ovoid mass (E)—the celiac axis bacterial aneurysm, approximately 4 cm. in longest diameter.

DISCUSSION

The two cases of coarctation of the aorta were unusual because both had bacterial aortitis with aneurysm formation and embolic glomerulonephritis.

The diagnosis of coarctation and aortitis was not made during life in either case. The clinical picture of severe renal damage held the attention of those treating Case 1. The observation of one doctor, that the systolic blood pressure was 30 degrees higher in the arms, apparently was given little attention in view of the absence of radiological and auscultatory signs of collateral circulation. Renal damage was considered to be the cause of the hypertension. The relatively afebrile course did not direct attention to the bacteriemia responsible for the embolic glomerulonephritis.

In Case 2 the bacteriemia was recognized. The patient was thought to have bacterial endocarditis superimposed on rheumatic endocarditis or an un-

designated type of congenital cardiac malformation. Again the insignificant collateral circulation produced no radiological, and only inconstant auscultatory, signs which might have led to the recognition of the coarctation.

Very often one reads or hears that the adult type of aortic coarctation is easy to diagnose, but surely this is not really true. Many cases do not provide the classical criteria. Doubtless some of these cases, not examined at autopsy, are finally diagnosed clinically as examples of malignant hypertension or some other condition.

The clinical signs of coarctation are well known and will not be reviewed here. Abbott¹ found no definite correspondence between the grade of coarctation or the extent of collateral circulation and the physical signs. Signs are not most prominent in the cases which present the most marked alteration in the physical characteristics of the aorta or the collateral vessels. Rib notching, often first discernible near maturity, increases with the passage of years. This is secondary to an alteration which increases with age in the physical characteristics of the collateral circulation. Several factors may be responsible for the variation in degree of discernible change in collateral vessels: (1) inherent qualities of the vessels, (2) grade of coarctation and degree of hypertension in the aorta proximal to the constriction, and (3) other physical characteristics, habits and environment of the individual. There is not a definite correspondence between rib notching and auscultatory evidence of collateral circulation. It is conceivable that a minimal grade of physical alteration is essential to the production of auscultatory signs in the collateral circulation and that a higher grade alteration will, in addition, produce rib notching after sufficient time has passed. Although these signs of collateral circulation may be coexistent, either may exist alone. Autopsy evidence of collateral circulation was found by Abbott¹ in only 56 of 129 cases of the adult type (in the literature). Cases have been reported showing: (1) significant coarctation with physical signs of collateral circulation but no autopsy evidence of physical alteration of collateral vessels, (2) significant coarctation with neither clinical nor autopsy evidence of collateral circulation, and (3) significant coarctation with slight clinical and marked autopsy evidence of collateral circulation. The cases reported herein fall into the second category.

Aortic coarctation really presents a complicated engineering problem. Careful analysis of all the factors concerned might enable one to improve the correlation between clinical and autopsy data. That all factors have not always been considered is obvious from the discrepancies which exist—the frequent missed diagnoses. Reliable quantitative data are desirable. There ought to be a correlation between quantitative data on coarctation cases and normal cases of the same age, race, and sex. It is not possible easily to accumulate sufficient material to illustrate this concept adequately, but we hope the following observations will lead others to undertake the major task or to add observations which will aid some future worker in the final synthesis.

Cardiac auscultatory findings in coarctation (systolic murmur at the base with or without a diastolic component) may be due in part to the passage of blood through the constricted portion of the aorta and in part to the abnormal currents of blood set up proximal to the constriction. Many observers have described dilatation of the proximal portion of the aorta. The presence of such dilatation might conceivably aid in the production of a murmur at the base. It might also be a factor of significance in the degree of development of a collateral circulation. So far as we can determine, quantitative measurements and comparison with a set of standard measurements have never been

made to establish as a fact the theory that dilatation of the ascending aorta exists in cases of coarctation. It is obvious that comparison must be made with a set of standards in order to rule out causes of dilatation other than the coarctation (arteriosclerosis, syphilis, etc.). Additional factors affecting both the degree of dilatation of the ascending aorta and the physical signs in a case of coarctation include: grade of coarctation, cardiac hypertrophy, extent of collateral circulation, coincident malformations (bicuspid aortic valve of Case 1), and other conditions.

In the two cases reported, measurements were made at loci which may be taken as standard points for use in any other case. Ten similarly preserved normal hearts and aortas from other white males 19 to 23 years of age were measured at each of the positions indicated in Table II, and the means established thereby were used as normals in determining whether there is dilatation in the specimens of coarctation. Three independent measurements were taken to the nearest millimeter. The figures in the table are in centimeters and, with the exception of the first, represent circumference. It is evident that the number of specimens used is insufficient for the establishment of ideal normal measurements for this age period. Nevertheless, the following conclusions seem justifiable. There is left ventricular hypertrophy in both Case 1 and Case 2. There is dilatation of the innominate ostium in Case 2, dilatation of the subclavian ostium in Case 1, stenosis in Case 2, and narrowing of the aorta at the subclavian level in both. There is no real dilatation of the aorta proximal to the coarctation. In neither case is it feasible to measure the aortic circumference between the ductus and the fourth intercostal artery because of the presence there of the aneurysm. Hypoplasia of the aorta below this level seems evident in Case 1.

Abbott² found a statement about dilatation in 129 of 200 cases she reviewed. Hypoplasia was reported in 21, normality in 7, and dilatation in 101 cases. "The cause of the dilatation of the aorta in this situation is no doubt in part the increased intravascular tension that exists in the upper part of the body above the stenosis, under which the great branches of the arch also become dilated and also atheromatous. . . ." Various other causes are considered contributory. Surely the pathogenesis will not be clearly understood until careful measurements have established the fact of dilatation and its relation to types and degrees of coarctation.

Bacterial Aneurysm.—Glomerulonephritis as a cause of death in coarctation of the aorta is not frequent. Probably in Case 1 an elevated blood pressure, caused by the coarctation, antedated the renal disease, while the glomerulonephritis was the result of long-standing bacteriemia from the bacterial aortitis. Death in uremia resulted from the extensive kidney impairment. A similar renal disease, but less extensive, occurred in Case 2. Death, in the second case, however, was from internal hemorrhage from one of the many bacterial aneurysms of arteries supplying the abdominal viscera. To be sure, the cause of death in both cases was intimately related to the aortitis. In both cases the aneurysm below the coarctation had progressed so far that it is fair to assume it might soon have ruptured. In Case 1 the esophageal mucosa comprised almost the entire remaining wall of the aneurysm.

In Case 2 four months before death a careful exploration of the mesentery at celiotomy showed no evidence of thrombosis. At autopsy, however, several large bacterial aneurysms with considerable thrombotic material were found. The small mass in the splenic artery might easily have been missed. If the aneurysm of the superior mesenteric artery had been present at that time, it

would have been discovered. Microscopically, the celiac axis aneurysm is the oldest. Had it been as large at the time of operation as it was at death, it could not have been missed. It is not unlikely that the symptoms which led to the celiotomy were produced by changes at this site, and that the mass later grew rapidly in size but was too small at that time to be palpated. Subsequently infected emboli broke off the thrombus in the celiac axis and lodged at numerous sites within the intrahepatic ramifications of the hepatic artery to produce the numerous bacterial aneurysms found there.

In Abbott's² 200 cases, bacterial endarteritis was present in 14. Death from rupture of the heart or aorta occurred in 40 cases; death from circulatory failure in 77 cases; and death from cerebral hemorrhage in 26 cases. Other causes of death were found in 43 cases.

From the literature as a whole are gleaned the cases outlined in Table III, in which an aortitis resulted in the formation of an aneurysm located just below the coarctation. Among these is the case of Kellogg and Biskind in which there was an additional bacterial aneurysm about 5 cm. from the origin of the superior mesenteric artery (compare with Case 2).

TABLE III. CASES OF COARCTATION WITH AORTIC ANEURYSM

AUTHOR	CASE	DEATH	ANEURYSM	COARCTATION	COMMENTS
1. Benecke	28 M	Cerebral hemorrhage	Directly below coarctation	Extreme stenosis beyond closed D.A. [*]	Glomerulonephritis
2. Evans Case 15	6 F	Rupture of aneurysm	Aortic end of closed D.A.	Moderate stenosis	Pneumococcus (?)
3. Focken Case 2	18 F	Septicemia	Directly below coarctation	Marked at closed D.A.	Glomerulonephritis streptococcus
4. Kellogg and Biskind	16 M	Cardiac failure	Directly below coarctation; superior mesenteric artery	Moderate. Slightly above patent D.A.	Aneurysm of superior mesenteric artery; streptococcus
5. Koletsky	38 M	Rupture of aneurysm	Directly below coarctation	Stenosis beyond D.A.	Acute glomerulonephritis
6. Libman, Abbott	12 F	Rupture of aneurysm into esophagus	Directly below coarctation perforating left bronchus	Moderate	Glomerulonephritis streptococcus
7. Reifenstein Case 2	10 M	Rupture of aneurysm into esophagus	Directly below coarctation, 3.5 by 5 cm. orifice	Marked 2.5 cm. —low sub-clavian	Pneumococcus
8. Smith and Hansmann	17 M	Rupture of aneurysm	1 cm. below coarctation, 6 cm. orifice	At closed D.A.	Streptococcus
9. Smith and Targett	9 M	Asphyxia cause by pressure of aneurysm	Directly below; 1.5 cm. orifice pressure on tracheal carina	Extreme at closed D.A.	Relation of aneurysm and esophagus like Case 1
0. Tillich	17 M	?	Directly below coarctation	Patent D.A. 4 mm. stenosis	Perforation of esophagus
1. Case 1	20 M	Uremia	Directly below coarctation	Marked	
2. Case 2	22 M	Intraperitoneal hemorrhage	Directly below coarctation	Moderate	

*D. A. = ductus arteriosus.

SUMMARY

Two cases of the adult type of aortic coarctation are presented. Anatomically these showed a moderate constriction and very little evidence of collateral circulation. Bacterial aortitis was present in both cases at the site of the coar-

tation. In one case the bacterial infection was recognized and a congenital cardiac malformation was suspected. The other case was characterized by hypertension and advanced signs of renal damage so that blood cultures were not done and a cardiac malformation was not suspected. Quantitative measurements of the aorta and the mouths of the innominate and the left subclavian arteries in these cases and in a group of controls provide a means for evolving a more careful definition of the anatomic changes in coarctation. A better correlation between clinical and autopsy data is needed because many cases of coarctation are missed clinically.

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RUPTURE OF VENTRICULAR MYOCARDIUM

REPORT OF FOUR CASES WITH COMMENTS ON PATHOGENESIS AND ON CLINICAL SIGNIFICANCE OF POSSIBILITY OF CARDIAC RUPTURE IN PROGNOSIS OF CORONARY ARTERY DISEASE

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SINCE coronary thrombosis became a popular clinical diagnosis, and the program of its treatment includes a minimum of six weeks' absolute rest in bed, cardiac rupture has loomed large in clinical thinking. The possibility of this complication in each case of myocardial infarction lends conviction to the argument which the physician advances in winning the cooperation of the patient and his attendants. The fear of cardiac rupture justifies sentencing the patient to being fed by spoon and to using a bedpan, even if there is a bathroom two steps away from his bed. How much of this fear is founded on fiction and how much on fact deserves serious reconsideration since, in the last twenty years, the diagnosis of coronary artery occlusion has become as popular as that of acute appendicitis, and the term coronary thrombosis has entered the vocabulary of laymen. The stories of these four cases of cardiac rupture may contribute something to the study of this problem.

CASE REPORTS

CASE 1 (a-21-28 M. G. H.).—A woman, aged 78 years, sustained a Pott's fracture Jan. 15, 1921. On the twenty-third day of rest in bed she had cardiac pain; on the twenty-seventh day there was a second episode of severe cardiac pain, with shock and death half an hour after onset. All the coronary arteries were found to be widely patent, except the anterior descending branch of the left coronary artery, which was greatly stenosed by arteriosclerotic plaques and occluded by a thrombus; there was a myocardial infarct in the anterior ventricular wall with rupture in this area and hemopericardium.

This patient was a well-preserved, somewhat obese lady, 78 years of age. The only illness she remembered was a right otitis media at the age of 76 years. On Jan. 15, 1921, while doing housework, she sustained a left Pott's fracture and was admitted to the surgical ward of the Montreal General Hospital, attended by Dr. Pennoyer. The left lower extremity was placed in a box splint, and, eleven days later, a plaster cast was applied. On the twenty-third day of this illness, she complained of "severe epigastric pain, belching of gas and pain in the cardiac region; colour became pale and flesh clammy; pulse was thready." Morphine sulfate, $\frac{1}{6}$ grain, soon relieved the pain and a soapsuds enema relieved the "gas." In the next four days she seemed to regain her usual health. On the twenty-seventh day of her stay in bed, at 7:30 P.M., she had "an attack of cardiac pain radiating to the shoulder and arm, along with some epigastric distress and belching of gas; very little dyspnoea. Pulse volume was full; rate, 110; rhythm, regular. Morphine sulphate, $\frac{1}{6}$ gr., was given for pain. At 8:00 P.M. she had some dyspnoea and became worse: skin was white and cold: pulse thready and then imperceptible in a few minutes, and so she died of acute cardiac dilatation."*

At this time I was associated with the Department of Pathology and it was my lot to perform the autopsy in this case. The following is an abstract of the report:

Post-mortem examination revealed considerable obesity, extensive bands of fibrous adhesions in both pleurae, fibrous adhesions about the spleen and liver, and kidneys of normal

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*These quotations are from the intern's notes in the hospital record.

size. There was a moderate degree of arteriosclerotic changes in the kidneys. Cardiovascular system: the maximum diameter of the heart in situ was 14 cm.; the pericardium was tensely distended, containing 200 c.c. of fluid blood and about 100 c.c. of blood clot. An abundance of epicardial fat was noted. The heart weight was 270 grams. On the anterior surface of the left ventricle, 5 cm. above the cardiac apex and just to the left of the interventricular groove, there was a transverse laceration 1.5 cm. wide (Fig. 1). A probe passed through this readily into the left ventricular cavity. There was no evidence of enlargement or hypertrophy. Slight arteriosclerosis of the aorta, mainly in its descending portion, was observed. The coronary artery orifices were patent and of normal size. The right coronary artery and its branches presented evidence of a slight degree of arteriosclerosis without stenosis. The left main coronary artery and its circumflex branch were similar to the right coronary artery. The anterior descending branch of the left coronary artery was greatly stenosed by large arteriosclerotic plaques, and, in the proximal third, it was occluded by an adherent recent thrombus.



Fig. 1.—Case 1. Anterior surface of ventricles: anterior descending branch of left coronary artery and some of its branches exposed. Note transverse tear in left ventricle. When opened longitudinally, the artery was found markedly stenosed by arteriosclerotic plaques in its whole length and occluded by a thrombus lying in its proximal third.

The smaller branches of this artery were also sclerosed. Microscopic examination in the region of the cardiac rupture revealed necrosis of muscle fibers, infiltration with masses of red blood cells, and also some inflammatory reaction manifested by the presence of leucocytes. Microscopic section of the myocardium of the left ventricle beyond the area of infarction revealed fatty infiltration of moderate degree and some increase in the width of the fibrous interstitial tissue.

Perhaps the clinical history is incomplete, but it has long been known that extensive arteriosclerotic disease of coronary arteries may exist for many years in some people without causing any symptoms. This patient illustrates this and also the fact that a myocardial infarct was established as a result of thrombosis of the only coronary artery that was affected by arteriosclerosis to a significant degree. Thus, in spite of ideal conditions for the development of collateral circulation, which would minimize the effect of sudden occlusion, infarction developed, and rupture of the myocardium occurred within the infarct.

Nor was bodily exertion an element of etiology for either the thrombotic occlusion or the myocardial rupture. The entire cardiac episode evolved while the patient was at rest in bed for the treatment of a Pott's fracture. The normal size of the heart supports the view that this patient had a normal or relatively low blood pressure. Thus the rupture must be explained mainly by processes of disease in the myocardium. On the fourth day after occlusion of the coronary artery, the infarct contained areas of myocardial degeneration of various sizes and shapes. Though the blood pressure was within normal limits, the thick ventricular wall was ruptured through the infarct. Small tears probably occur very commonly in myocardial infarcts, but in this instance the plane in which the tear was initiated led to its extension, until it reached the epicardial surface. The last half hour of the patient's life was most likely the period in which the epicardium was torn and the cardiac tamponade developed.

CASE 2 (J. G. H. A44-838).—A man, aged 61 years, experienced three episodes of myocardial infarction in thirty months. The first two were untreated at the onset and subsequently treated with rest in bed; the third was recognized at the onset and treated with strong sedatives and absolute rest in bed. Rupture of the myocardium occurred, followed by death on the fifth day of the third episode.

First Episode.—This man was in good health until the age of 59 years, when, in July, 1941, he began to have pain in the left shoulder and profuse sweating, which wakened him from sleep almost every night. On Nov. 21, 1941, at 2:00 A.M. he woke feeling severe "soreness" under the lower two-thirds of the sternum and in the left shoulder and arm. He had some nausea but could not vomit. He perspired profusely. At 6:00 A.M. Dr. Mingie saw him, diagnosed coronary thrombosis, and ordered rest in bed for several weeks. However, the patient ignored this advice and, on the following day, returned to his work as an executive in a factory. On November 23, he shovelled snow to clear his garage driveway. He felt he had a mild cold on November 24, and remained at home that day and the next. He first consulted me on November 26, not because he felt sick, but to placate his family. He had not had any previous illness. In his business affairs he had had many ups and downs, and, since 1940, they had been in a serious state of depression.

Physical examination revealed a rather slender, agile man, 5 feet, 5 inches, in height and weighing 140 pounds; his complexion was pale. There was no anemia; the liver edge could be felt 6 cm. below the costal border on deep inspiration; and the lung signs were normal. An orthodiagram of the heart revealed: aortic arch, 4.5 cm.; right border, 5 cm.; left border, 7.8 cm.; transverse diameter of chest, 27 cm.; and aorta, somewhat elongated. The heart sounds were normal except for an amphoric quality of the second sound at the apex. A faint systolic murmur between the first and second sounds was heard all over the precordium, and a very faint diastolic murmur immediately after the second sound at the left border of the sternum between the fourth and sixth costal cartilages was also observed. The blood pressure was 106/66 (Fig. 2); neurological signs, normal; fundi, moderate tortuosity of retinal arteries; urine, specific gravity, 1.020 (no sugar or albumin); blood Wassermann, negative. An electrocardiogram (Fig. 3A) revealed no evidence of recent or old myocardial infarct and a left axis deviation, suggestive of some left ventricular enlargement. He remained at home in bed (with bathroom privileges) during the next six days, and then entered the Western Division of the Montreal General Hospital for further investigation. Studies made in the course of fifteen days revealed no fever; four white cell counts between 6,400 and 7,900; four sedimentation velocity determinations, 0.5 to 0.65 (normal 0.08 to 0.38 mm. per minute); and seven electrocardiograms revealed slight variations in amplitude of positive T in Leads I and II, more marked variations from positive to negative T in Lead III and a normal CF₂ (Fig. 3).

Diagnosis: arteriosclerotic (and probably hypertensive) heart disease; coronary arteriosclerosis with stenosis; occlusion of a coronary artery with myocardial infarction; and moderate left ventricular enlargement. He remained at home in bed (with bathroom privileges) for another six weeks, then convalesced for several weeks. He frequently had pain in the right shoulder on movement of this joint, usually before changes in the weather. Physical examination on June 25, 1942, revealed no new feature, except that the blood pressure was 150/80; the electrocardiogram was similar to the previous record. During the next year and one-half he rarely had substernal discomfort; if it occurred on hurried walking, it

was quickly relieved by rest or, if initiated by excitement, by moving away from the scene. He did not require nitroglycerin and took no other medication. On July 23, 1943, an electrocardiogram recorded by Dr. H. Shister was similar to the record of June, 1942.

Second Episode.—On Dec. 19, 1943, at 2:00 A.M. the patient was awakened from sleep with pain under the mid-sternum and in the left arm. His forehead was "wet and cold." A nitroglycerin tablet taken on wakening seemed to produce relief in a "few" minutes ("perhaps three minutes"); the ache in the left arm was last to disappear. The patient continued at work as usual and consulted me for a "periodic check-up" on Dec. 22, 1943. His general appearance was good; new features as compared with observations of June, 1942, were: diminution in loudness of the first heart sound; blood pressure, 160/98; and a grossly abnormal electrocardiogram, showing inversion of T_1 , almost isoelectric T_2 , inversion of T in Leads CF_2 and CF_4 . This brief cardiac pain did not justify the diagnosis of coronary artery occlusion, rather did it suggest prodromal symptoms, perhaps due to hemorrhage into an arteriosclerotic plaque causing stenosis of a large coronary artery. Rest in bed (with bathroom privileges) for a month was prescribed. On Jan. 18, 1944, he reported he had had no discomfort during this month. His blood pressure was 130/80; the first sound appeared louder than on Dec. 22, 1943, but less loud than in June, 1942; an unusually prominent and forceful pulsation in the fifth left intercostal space near the sternum suggested aneurysm of the anterior ventricular wall; and the electrocardiogram was similar to that of Dec. 22, 1943. It was thought that the new infarct in the anterior ventricular wall had occurred "painlessly" at some time between July and Dec. 22, 1943. He was permitted to resume light activities in his business and was free from symptoms for one month.

Third Episode.—On Feb. 17, 1944, he slept soundly from 10:00 P.M. to 4:00 A.M., when he awoke with severe pain in the interscapular region, marked sweating, and some substernal aching. Nitroglycerin did not relieve this pain. He waited until 7:00 A.M. to call me and was given morphine sulfate, $\frac{1}{4}$ grain, hypodermically at 7:30 A.M. by Dr. Golfman. This relieved the pain to a considerable degree and made him drowsy and nauseated. When I saw him at 10:00 A.M. he appeared paler and more sallow of complexion than usual; he had some aching under the sternum and was drowsy. His blood pressure was 120/90, but the brachial artery sounds were faint, suggesting reduced volume of cardiac output per beat. Faint heart sounds and a blowing systolic murmur, loudest at the apex and at the left border of the sternum near the fourth intercostal space, suggestive of mitral insufficiency, were new features. An electrocardiogram showed gross changes indicative of recent ventricular infarct. The systolic murmur suggested infarction and perhaps tearing of a papillary muscle in the left ventricle. During the day of February 17 he awakened frequently with moderately severe pain, interscapular and substernal, of several minutes to a half hour in duration until he dozed off again. He was given $\frac{1}{4}$ grain of morphine sulfate at 10:00 P.M. and slept well after 11:00 P.M. On February 18 he was free from pain or dyspnea and at 10:00 P.M. his blood pressure was 110/84; the heart sounds and the murmur were almost the same as on February 17. On February 19, at about 8:00 A.M., he began to have dyspnea; at 9:30 A.M. moist râles were heard at both bases by Dr. Golfman, who, however, found no indication for morphine and prescribed $\frac{1}{4}$ grain of codeine phosphate as a sedative. At about 3:00 P.M. he became acutely and severely dyspneic, very restless, and apprehensive. At 4:45 P.M., I observed marked cyanosis of hands and feet; coldness of the skin; continual moderate sweating; marked orthopnea; rapid, rather shallow respiration; marked anxiety; blood pressure, 104/90; and very faint brachial artery sounds. Auscultation of the heart revealed a rapid rate (140) and faint heart sounds, almost inaudible at the apex and the base, but the chief feature was a loud systolic murmur with a new, "whee jee wee"-like quality, loudest at the right border of the sternum. In thinking of how to describe this murmur, I thought it sounded like the noise produced in squeezing raw meat. This led to the thought that the new developments in the clinical picture might be due to rupture of the myocardium. The murmur was not loud enough to justify placing the site of the rupture in the interventricular septum but was suggestive of rupture of the ventricular wall with a slow leak through the almost intact pericardium. Electrocardiograms taken on February 18 and 19 suggested anterior wall infarction, and reduction in the amplitude of QRS was compatible with pericardial effusion. Satisfactory percussion revealed no change in the heart size to confirm the suspicion of hemo-pericardium. The absence of a diastolic phase of the murmur suggested that the peculiar quality of the murmur did not represent a friction murmur, but this possibility could not be ruled out entirely. At 6:00 P.M. he was admitted to the Jewish General Hospital. At 11:00 P.M. only a faint systolic murmur at the left border of the sternum could be detected, and our opinion favored pericarditis as the cause of the unusual murmur that was heard earlier.

The systolic blood pressure was now only 30; the brachial artery sounds were extremely faint, and the radial pulse was extremely small. Cyanosis of the extremities persisted, although the patient had been in an oxygen tent for about five hours. The suspicion of ventricular rupture inhibited me from giving blood plasma for the treatment of shock. The next day, about twenty-eight hours after the onset of this grave phase of the illness (with anuria present

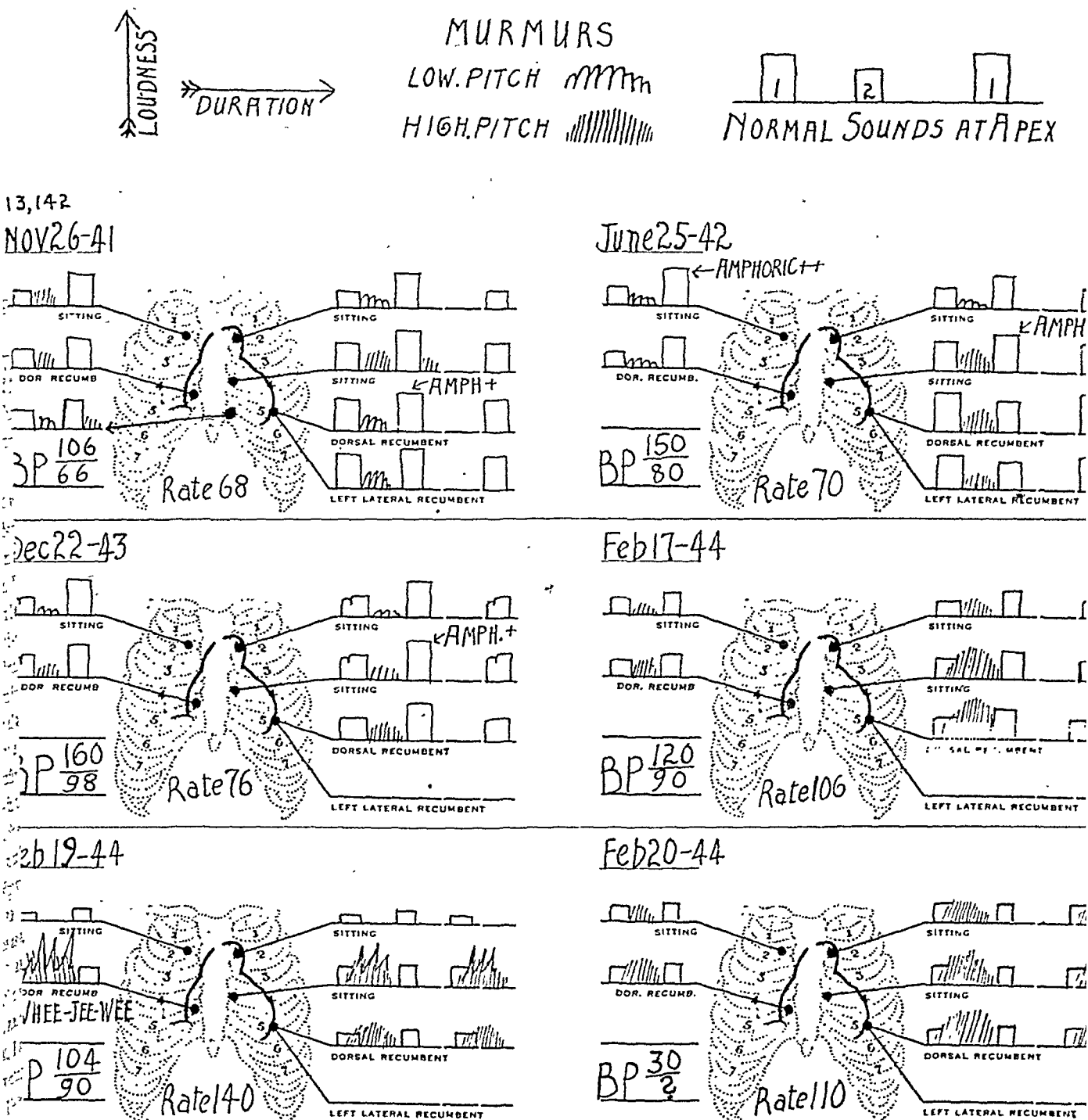


Fig. 2.—Case 2. Heart sounds and murmurs. Nov. 26, 1941: Amphoric second sound at apex suggests a large gas bubble in stomach; faint aortic insufficiency murmur was heard only on this day and suggests transient aortic insufficiency of slight degree or pericardial friction murmur. Systolic murmur not loud or long enough to be evidence of valvular disease.

June 25, 1942: Amphoric second sound a new feature, suggests arteriosclerosis with some dilatation of ascending aorta.

Dec. 22, 1943: Only minor variations observed until this date, when the first sound was much less loud than formerly with no change in the second sound. Electrocardiogram revealed evidence of recent myocardial infarct near cardiac apex in anterior wall.

Feb. 17, 1944: Seven hours after onset of third episode of myocardial infarction during which rupture of myocardium occurred. Loud systolic murmur indicative of mitral insufficiency suggests diagnosis of torn papillary muscle.

Feb. 19, 1944: Heart sounds very faint, heard only during sustained expiration, but peculiar "whee-jee-wee" murmur together with systolic murmur of mitral insufficiency was readily audible. This peculiar murmur suggested rupture of ventricular wall, but was probably a pericardial friction sound.

Feb. 20, 1944: At one time on this day (twelve hours before death) the systolic murmur of mitral insufficiency was quite loud, although blood pressure was very low; later the murmur and heart sounds became very faint.

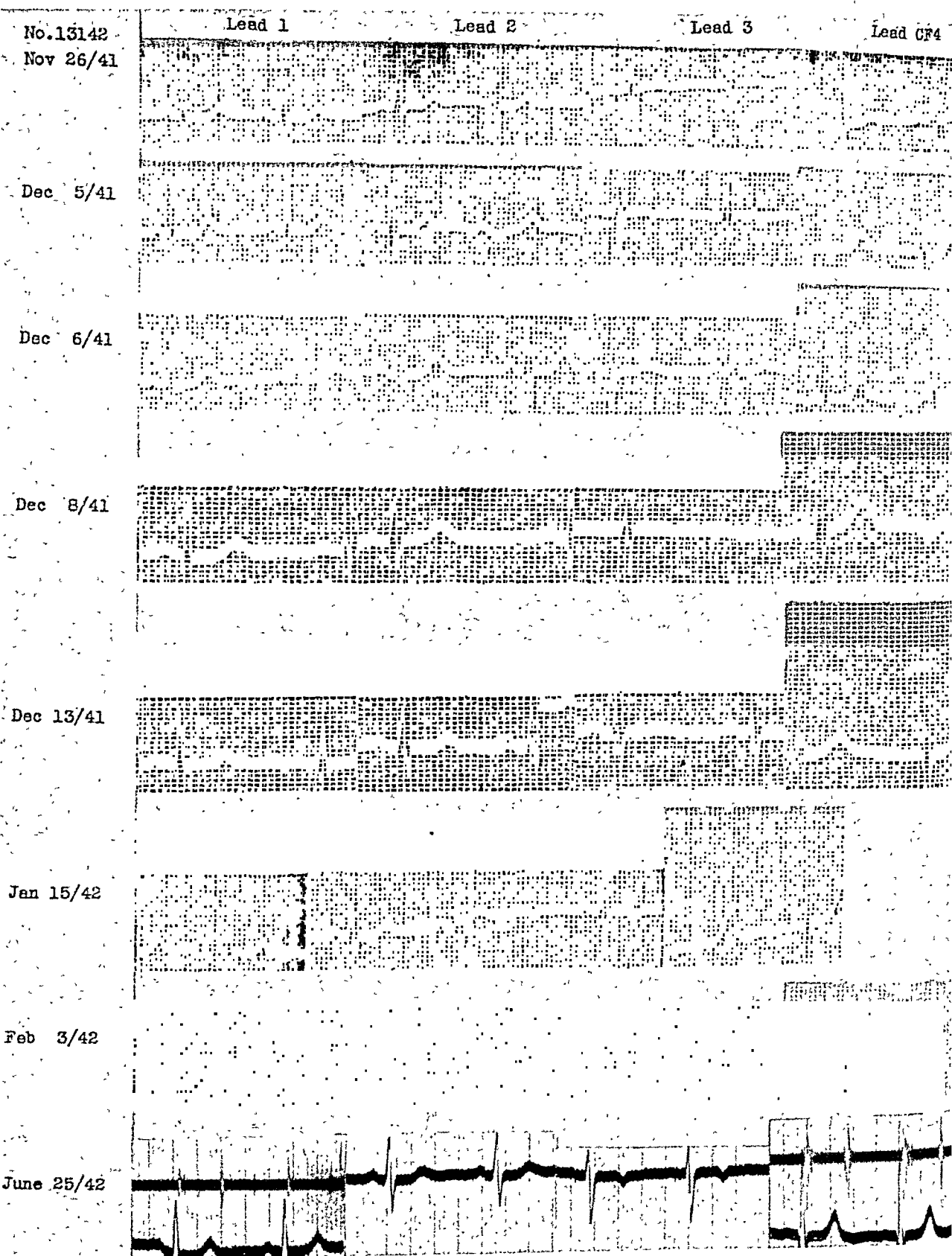


Fig. 3A.—Case 2. The six records made between Nov. 26, 1941, and Jan. 15, 1942, were selected from eight made in this period. They show slight variations in the S-T segment of Leads I and II, changes in T of Lead III from positive to negative and variations in amplitude of T in CF₄. These minor abnormalities were related to healing and fibrosis of an infarct in the central portion of the interventricular septum. The records of Feb. 3, 1942, and June 25, 1942, show very slight changes in T of Lead III.

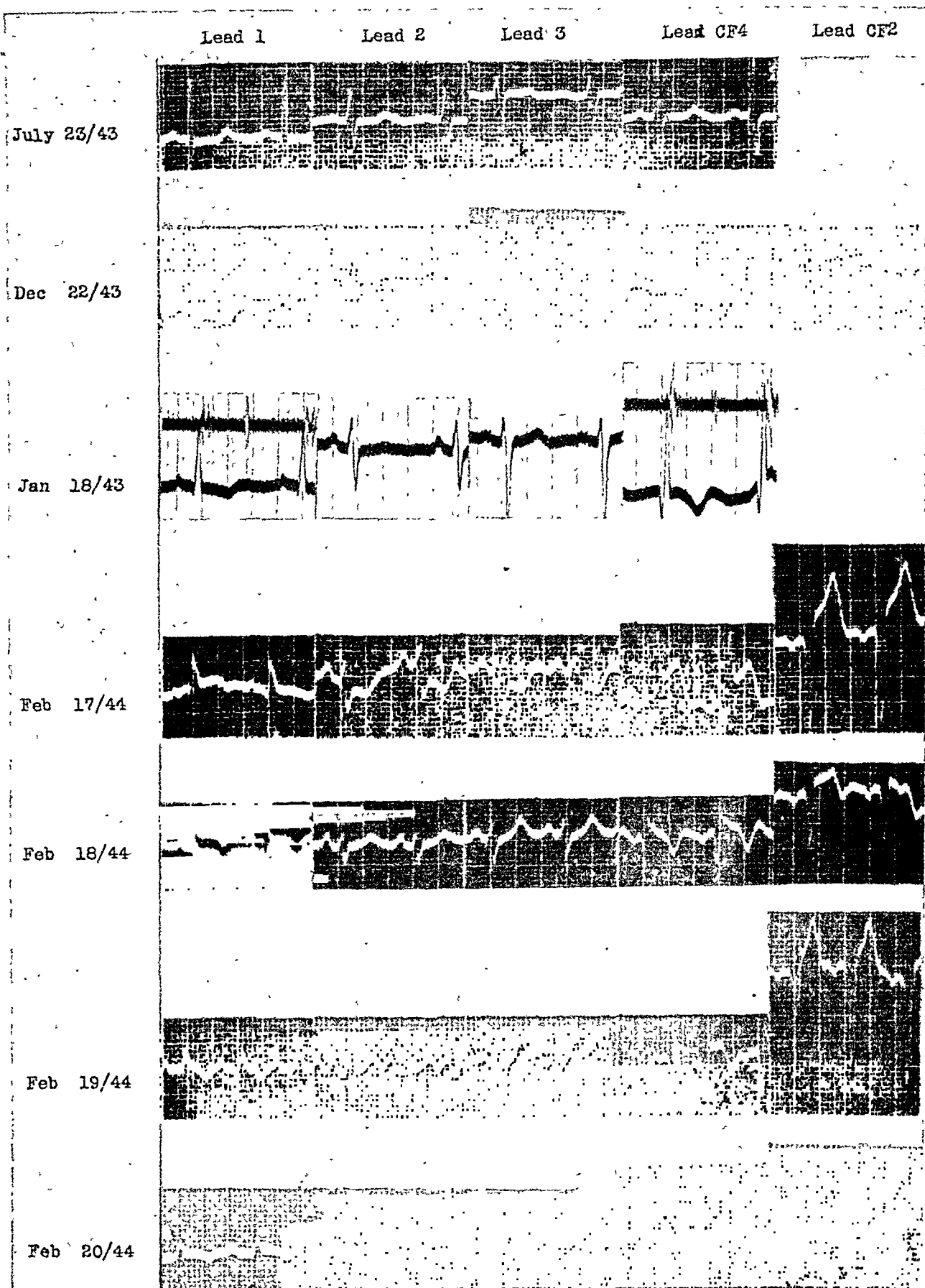


Fig. 3B.—Case 2. The record of July 23, 1943, is similar to that of Dec. 6, 1941, with positive T waves in Lead III. The first gross abnormalities appear in the records of Dec. 22, 1943, and Jan. 18, 1944. They are related to infarction of the anterior wall of left ventricle with aneurysmal dilatation near the apex. Note diphasic T in Lead I, low voltage of T in Lead II, high T in lead III, and inverted T in CF₄ and CF₂. The amplitude of R in Lead I and S in Lead III have increased, suggesting left ventricular enlargement. In the record of Jan. 18, 1944, the phonocardiogram recorded simultaneously with Lead CF₄ represents the heart sounds over the region of the fourth intercostal space, near the sternum; an auricular sound of low amplitude was recorded on this day, which was not audible during ordinary auscultation and was not recorded in June, 1942. This new feature probably represents the effect of thinning of the left ventricular wall near the apex, following infarction about a month or more previously.

The last four records represent the effects of thrombosis of the left circumflex branch of the left coronary artery with infarction in the left ventricle at its left margin and posteriorly, tearing of the anterior papillary muscle near its base, rupture of the left ventricle and hemopericardium. There is no specific feature to suggest rupture of the myocardium. Changes from negative to positive T in Lead CF₄ point to involvement of the posterior ventricular wall.

during all this time) persistence of the blood pressure at about 30 mm. led to the decision that 500 c.c. of a 10 per cent glucose solution should be given and should be followed by plasma until the blood pressure would rise, or until, as expected, the patient would die. Percussion again failed to reveal any sign of pericardial effusion, and there was no pericardial friction murmur, but only the blowing systolic murmur which suggested rupture of a papillary muscle causing mitral insufficiency. He remained mentally clear until about six hours before his death, which occurred at 4:00 A.M., Feb. 21, 1944, ninety-six hours after the onset of the final illness and thirty-seven hours after the beginning of the terminal grave phase. Pulmonary edema and unconsciousness developed gradually in the last six hours. The autopsy was performed by Dr. M. Simon and the following is an abstract of the report.

The right pleural cavity contained 300 c.c., and the left 200 c.c., of straw-colored fluid with a specific gravity of 1.010. There was a moderate degree of pulmonary edema; the abdominal viscera showed evidence of a mild degree of chronic passive hyperemia. The heart (Fig. 4) was enlarged (510 grams); the pericardium appeared somewhat tense and, on being opened, revealed a thin layer of dark red blood covering the whole surface of the heart; a thin, sticky, fibrinous exudate bound the pericardial surfaces, particularly over the anterior aspect of the heart. A poorly defined bulge about 3 cm. in diameter was found near the apex of the left ventricle; on the anterior surface of the left margin of the left ventricle, about 6 cm. from the apex, a mottled yellow and red depression, about 4 mm. in diameter, was present; a fine probe passed through this depression into the left ventricular cavity leading to the base of the anterior papillary muscles. This track lay in a recent infarct. The anterior left ventricular wall for a distance of about 5 cm. above the apex was yellowish red, mottled, and friable. Section through the interventricular septum revealed the appearance of extensive fibrosis, evidence of an old, healed infarction. There was a mural thrombus at the bulging area near the left ventricular apex and a smaller (2 cm. in diameter) thrombus in the left auricular appendage. The valves revealed no abnormalities. The left circumflex artery was markedly sclerosed and, beginning 2 cm. from its origin, there was an adherent red thrombus which extended into and occluded several of its medium-sized branches, which lay in the area of recent infarction. The anterior descending ramus of the left coronary artery was markedly stenosed by arteriosclerotic plaques. At a point 1 cm. from its origin, section revealed only a pin point eccentric lumen. Below this point sections revealed no gross evidence of any lumen. The right coronary artery was less extensively sclerosed, but at a point 2 cm. from its origin, there was a thick arteriosclerotic plaque, reducing the lumen to about one-third of the diameter of the artery. The aorta revealed arteriosclerosis, most marked in the lower abdominal region and extending into the iliac arteries.

Microscopic examination of a section of the left anterior descending branch of the left coronary artery showed extensive calcification of the media and numerous atheromatous plaques containing acicular slits. About one of the larger plaques, numerous phagocytes filled with golden-brown, granular pigment were noted. There was also evidence suggesting canalization of an old thrombus. Section through the left circumflex branch of the left coronary artery revealed a markedly thickened, partially calcified wall containing a large atheromatous plaque. The lumen was completely occluded by a laminated recent thrombus. Section through the left ventricle at the site of the perforation showed extensive necrosis of the myocardium, interstitial hemorrhages and a diffuse infiltration by large numbers of polymorphonuclear leucocytes. Between the columnae carnae a large laminated recent thrombus was present. At some distance from the area of recent infarction focal areas of fibrosis were seen in the myocardium.

Correlation of clinical observations and thoughts with what was found at autopsy suggests that the peculiar "whee-jee-wee" systolic murmur (Fig. 2) was more likely due to pericardial fibrin deposits from blood which had oozed slowly into the pericardial cavity than to blood squeezing through the track of ventricular rupture. This murmur did not bear any resemblance to that described by Reznikoff⁹ in a case of a ruptured anterior wall of the left ventricle, following coronary thrombosis. The murmur was heard best near the fourth and fifth right costal cartilages over the right auricle and the right border of the right ventricle; the pericardial end of the ruptured ventricle was far to the left, on the left cardiac border in the vicinity of the fourth left rib, about 7 cm. from the mid-sternal line. Only by imagining a peculiar effect of the stream of

ejected blood coming through the pericardium, so that the murmur was produced near the right border of the heart, instead of over the area of the rupture, could one relate the murmur to the rupture. This must be considered an unlikely possibility. Thus, the ante-mortem diagnosis of cardiac rupture was made in part on false premises. Moreover, the site of the rupture was not as predicted, for it was thought that it would involve the aneurysmal dilatation which seemed to be in the anterior ventricular wall to the right of the cardiac apex. The aneurysmal dilatation near the cardiac apex was intact and occupied by an old, adherent laminated thrombus.

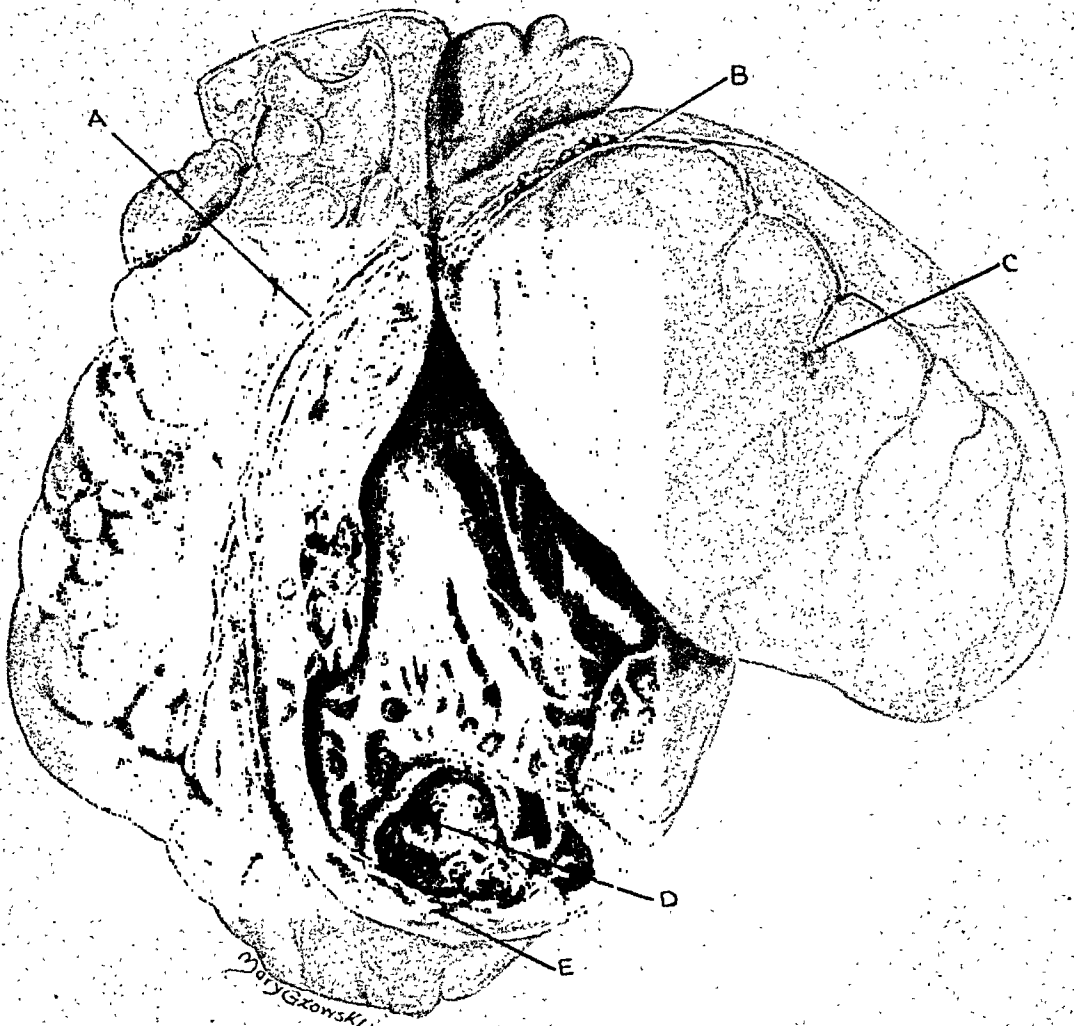


Fig. 4.—Case 2. A, Stenosed anterior descending branch of the left coronary artery. B, Thrombus in circumflex branch of the left coronary artery. C, Site of rupture. D, Mural thrombus. E, Aneurysm of anterior wall of left ventricle.

It is most likely that tearing of the myocardium began soon after occlusion of the left circumflex coronary artery and that the initial tears involved the base of the left anterior papillary muscle, resulting in some mitral insufficiency which revealed itself by the loud, blowing, systolic murmur. Some degree of shock was present from the beginning of this episode, but the severe degree which began about thirty-seven hours before death could have been coincident with progressive extension of the track of tearing until it reached the pericardium, when acute dyspnea, chest pain, marked fall in blood pressure, cold extremities, etc., set in. The thin layer of bloody fluid in the pericardium must have accumulated slowly in this period of about thirty-seven hours and was not enough to cause cardiac tamponade. It appears most probable that death was a direct sequence of the state of shock rather than a direct result of the cardiac rupture.

The state of shock was initiated primarily by thrombotic occlusion of the left circumflex coronary artery and probably aggravated by the process of myocardial tearing to the point of rupture through the pericardium.

The marked fibrosis in the interventricular septum probably represents the site of myocardial infarction during the first illness in November, 1941. It is of interest that the electrocardiograms related to this revealed only minor abnormalities of T waves in Lead III and no notching or prolongation of QRS (Fig. 3). The infarction near the apex of the left ventricle, resulting in a slight aneurysmal dilatation, occurred almost painlessly at some time between July and Dec. 22, 1943. The attack of cardiac pain, which woke him from sleep on Dec. 19, 1943, and which lasted about three minutes and was relieved by nitroglycerin, did not suggest coronary artery occlusion with myocardial infarction. It was interpreted as evidence of considerable arteriosclerotic stenosis of one of the larger coronary arteries. A small hemorrhage into an arteriosclerotic plaque was visualized, and a program of rest in bed for several weeks was advised, because this event was looked upon as possibly prodromal to coronary artery occlusion. Microscopic examination of the ventricular muscle in this region revealed evidence of active disease, indicating that the infarct was relatively recent. It now appears most likely that the brief episode of pain did represent occlusion of the considerably stenosed anterior descending branch of the left coronary artery. Thus, about two months after this had occurred, fibrosis of the infarct was not yet complete. This slow healing may in part account for the development of some aneurysmal dilatation which was detected clinically a month after the infarct was initiated.

The anatomic findings do not provide an adequate explanation for some features of the clinical picture. There is the fact that the earliest symptoms of impaired coronary circulation occurred at night, wakening the patient from sleep, and consisted of transitory left shoulder pain with profuse sweating. Much later and only after the first episode of coronary artery occlusion, did he begin to suffer from the more common symptom-complex of substernal and left-arm pain on hurried walking, or as a result of acute excitement. Also, the first attack was not associated with the development of shock, the second was almost symptomless, and the third, the only one that was treated in orthodox fashion from the beginning, led to shock and was complicated by rupture of the ventricle, terminating fatally. These problems are mentioned in order to indicate that knowledge of the morphology of the heart and blood vessels does not solve them; the correct answers must await a fuller knowledge of pathologic physiology. The initiation of cardiac pain, by acute excitement such as anxiety, or by a sense of hurry as when the individual fears he may be late in reaching his destination as he sits comfortably in a vehicle, are familiar psychosomatic phenomena. It has been shown that in the dog¹ the vagus nerve acts as a vasoconstrictor for the coronary arteries, and that central or reflex increase in tone of the vagus center causes reduction in the quantity of blood flow through coronary circulation. These facts lead one to search for the psychic phenomena which may occur during sleep and which would increase vagus tone. Such knowledge might account for the central and reflex type of coronary vasoconstriction. Recently, Waugh and Ruddick¹² have reported that during uncomplicated rest in bed there is an increase in coagulability of blood. This fact may eventually be associated with others, which might explain the occurrence of coronary artery thrombosis during absolute rest or during sleep, as in three of these four cases.

CASE 3 (J. G. H. 23729).—A woman, aged 67 years, was admitted for investigation of intestinal hemorrhage and anemia. Carcinoma of the cecum was found. Acute weakness and chest pain, lasting about an hour, occurred six days before sudden death. Autopsy revealed embolus of vegetation from the mitral valve to the left circumflex branch of the left coronary artery and rupture of the left ventricle.

A small, pale, poorly nourished woman of 67 years, weighing about 80 pounds, had seen blood in her stools occasionally for some years and more frequently for some months before admission. She had had arthritic aches and pains for many years, but no cardiac symptoms. Physical examination revealed slight cardiac enlargement and a blowing systolic murmur, loudest at the apex, partially masking the latter half of the first sound and suggestive of mitral insufficiency. Her blood pressure was 150/80. The cecum appeared to be rather broad; large external and internal hemorrhoids were observed; gastric analysis was normal. An x-ray examination suggested a lesion in the lower pole of the cecum and calcification in the aortic valve. Hemogram: 2.9 million red cells; 39 per cent hemoglobin; 9,400 white cells; and 83 per cent polymorphonuclear. Blood Wassermann was negative. Fasting blood sugar was 108 mg. per cent; nonprotein nitrogen was 24 mg. per cent. On July 10, 1940 (the sixth day in the hospital), at 8:30 A.M. the patient suddenly felt very weak. She had pain in the left breast region; the pulse was weak, rate, 42. Some pain persisted for about an hour and she had weakness during the whole day. Her blood pressure was 136/70 at 10:00 A.M. She had a barium enema in the afternoon. A transfusion of 300 c.c. of blood was given the following day. The stools contained large amounts of dark red blood. During the next five days she had no pain in the chest but was weak and drowsy until sudden death occurred at 10:30 A.M., about a half-hour after an effectual enema that had not caused any discomfort. The patient had been constantly in bed while in the hospital for twelve days.

Clinical Diagnosis: Carcinoma of the cecum; severe hypochromic anemia; large hemorrhoids; general arteriosclerosis; moderate cardiac enlargement; mitral insufficiency; and calcification of the aortic valve. The autopsy was performed by Dr. M. Simon, and the following is an abstract of his report.

Well differentiated adenocarcinoma of the cecum was present near the ileocecal valve; there were metastases to the peritoneum, spleen, omentum, and lymph nodes at the porta hepatis. Pulmonary emphysema and internal and external hemorrhoids were observed. Cardiovascular system: the pericardium contained about 300 c.c. of pale, watery, blood-tinged fluid; the heart was of average size; the epicardium was normal; and a small amount of subepicardial fat was present. At about the middle of the posterior wall of the left ventricle a linear tear, 12 mm. long, was observed; a probe passed through this tear into the left ventricle. The endocardium of the left auricle was somewhat opaque and wrinkled; the mitral valve appeared slightly thickened and there was slight fusion of the leaflets: just above the line of closure, on the auricular surface of both leaflets, there were four small pinkish-yellow vegetations (3 to 4 mm. in diameter). The endocardial end of the cardiac rupture was 3 mm. in diameter, situated behind the posterior leaflet of the mitral valve, nearer the base than the apex of the left ventricle. The cut surface of the myocardium in the vicinity of the tear showed slight reddish-yellow mottling. There was a slight fusion of the left coronary and the noncoronary cusps at the aortic valve for a distance of about 3 mm. at the commissure. The circumflex branch of the left coronary artery was somewhat larger than normal. At a point about 3 cm. from its origin, and where it gives off a branch which goes to the region of the myocardial tear, there was a pinkish-yellow, adherent mass of material which resembled the mitral valve vegetations and completely occluded the arterial lumen. The remainder of the coronary arteries revealed slight to moderate degree of arteriosclerosis. Microscopic examination of the embolus and of the mitral valve vegetations showed them to be similar, pink-staining amorphous material with focal collections of polymorphonuclear leucocytes and strands of fibrin and no bacteria. In the region of the tear, the myocardium revealed only slight hemorrhage along its edges and extensive replacement of muscle fibers by granulation tissue, containing fibroblasts and histiocytes, many containing golden-brown granular pigment. At some distance from the margin of the tear, there were foci of myocardial necrosis containing polymorphonuclear leucocytes. At only one point near the edge of the tear, the connective tissue about a thick-walled artery contained histiocytes, lymphocytes, and occasional polymorphonuclear leucocytes. This resembled an Aschoff body. Elsewhere in the myocardium no Aschoff bodies were found.

The significance of the acute episode of weakness, bradycardia, and pain in the left breast region, which occurred six days before death, was not recog-

nized. It was considered as part of the clinical picture of arthritic pain in an emaciated old lady, suffering also from marked anemia, associated with carcinoma of the cecum. If electrocardiograms had been recorded in the interval of six days before death, the diagnosis of myocardial infarction probably due to coronary thrombosis might have been made. The sudden death might have been associated with this diagnosis. Death occurred within about two minutes after the patient suddenly appeared gravely ill with labored breathing and a very small, thready pulse. There was no indication of severe pain. The epicardial opening was 12 mm. and the endocardial, 3 mm. in length. This suggests that cardiac tamponade developed rapidly. Except for the x-ray examination of the lower bowel, which was carried out in the dorsal recumbent posture, this patient had not been disturbed by any special studies and remained constantly in bed. This did not prevent evolution of infarction and rupture of the myocardium. Moreover, there was no hypertension. If the myocardial infarct had been recognized, sudden death on the sixth day might have justified considering the possibility of cardiac rupture as the cause of death, but other possibilities such as ventricular fibrillation, occlusion of a large coronary artery, etc., also existed.

CASE 4 (M. G. H. A-44-41).—A man, aged 61 years, had hypertension for more than three years. Twenty days before death he began to have cardiac pain only on walking outdoors. For eleven hours before death he had severe cardiac pain. Autopsy revealed rupture of the anterior wall, involving both ventricles and the interventricular septum and probable rupture of the coronary artery.

This man was a machinist. He had had pneumonia at the age of 27 years. On April 17, 1941, at the age of 58 years, he experienced numbness and weakness of his left hand for several hours, and his blood pressure was 172/90. These symptoms lasted only one day. Blood Wassermann reaction was negative. On Jan. 25, 1944, he began to have pain across both shoulders posteriorly and under the lower front of the chest after walking outdoors for a few minutes. This came on more readily soon after meals than when the stomach was empty; stopping to rest for a minute or two brought relief. The patient experienced no discomfort indoors, either at work or rest. Physical examination, Feb. 8, 1944, he appeared younger than 61 years and could pass for 50; his weight was 152 pounds, and his height, 5 feet, 5 inches. Neurological signs were normal; the liver edge was felt 4 cm. below the costal border on deep inspiration; and the lung signs were normal. A forceful cardiac apex impulse in the fifth left intercostal space, 9 cm. from the midsternal line, suggested some cardiac enlargement. The second heart sound had an amphoric quality at the apical and tricuspid areas only; no other abnormalities of heart sound were heard. Blood pressure was 210/110. An electrocardiogram showed normal rhythm; rate, 56; P-R, 0.16 second; QRS, 0.08 second; slurred R in Leads I and II; left axis deviation, suggestive of left ventricular enlargement; and inverted T in CF, suggestive of myocardial disease in anterior ventricular wall.

Diagnosis: arteriosclerotic and hypertensive cardiovascular disease; left ventricular enlargement; coronary arteriosclerosis; prodromal stage of coronary artery occlusion.

Treatment: rest in bed (with bathroom privileges); $\frac{1}{400}$ grain of nitroglycerin for relief of pain, and triturate of morphine sulfate, $\frac{1}{4}$ grain, to be taken while awaiting arrival of physician if nitroglycerin failed to relieve pain. Phenaminophyllin (phenobarbital, $\frac{1}{4}$ grain, and aminophyllin, $1\frac{1}{2}$ grains), one tablet every four hours four times a day, was prescribed.

The patient remained at home, but not constantly in bed on February 9, 10, and 11, and then, contrary to advice, worked (without discomfort) on February 12. He felt well on Sunday, February 13. On Monday, February 14, whilst in a streetcar on his way to work he began to have very severe pain across the front of the chest and in both shoulders and arms. He returned by streetcar and walked about one-eighth of a mile from the streetcar to his home, arriving in a state of shock. The pain persisted and grew in intensity; he perspired profusely and his color was ashen gray during the sixty minutes he spent on this journey. After reaching his home, at 8:00 A.M., he initiated vomiting by putting his finger in his throat; this gave no relief. Vomiting recurred spontaneously and his wife reported

she observed clots of blood in the vomitus. His physician, Dr. Nelligan, came at 10:30 A.M. and found signs of shock. Scarcity of hospital beds delayed his admission to a hospital, until he was brought to the Montreal General Hospital at 5:30 P.M. The pain had persisted all day. He had no dyspnea and he remained clear mentally while in the ambulance. About five minutes after reaching the hospital and while still on the carrier stretcher in the admitting officer's examining room, he suddenly expired. The autopsy was performed by Dr. J. Pritchard, and the following is an abstract of his report.

Both pleural cavities were almost entirely obliterated by fibrous adhesions; there was no evidence of hemorrhage in the gastrointestinal tract; and no evidence of renal arteriolar sclerosis was found. Numerous liver cell nuclei revealed glycogen vacuolization. One small area of hemorrhage and one of softening appeared in microscopic sections of the hypothalamus. Cardiovascular system: maximum transverse diameter of the heart in situ was 13 cm. and of the chest cavity, 28 centimeters. The pericardium was adherent anteriorly to the sternum and the pericardial cavity contained 300 c.c. of blood and clot. On the anterior surface over the region of the interventricular groove at a point 5 cm. from the apex, a perforation 1 cm. in diameter was found; its edges were ragged and the muscle surrounding it, soft and flabby. A probe passing through it could enter either the right or left ventricle.



Fig. 5.—Case 4. Cross-section of left anterior descending branch of the left coronary artery, through the region which grossly appeared to contain the thrombus and is situated in the vicinity of cardiac rupture. Considerable lymphocytic infiltration in adventitia; on one side a large atheromatous plaque lies in the thickened fibrosed intima; the media over this plaque is very thin and atrophic; opposite this plaque the continuity of the arterial wall is broken by what appears to be a "blow-out" with edges turned outward. In and near the thick intima there is marked hematoxylin staining of tissue suggesting iron, the remains of old hemorrhage. In the arteriosclerotic plaque there are foam cells, many free red blood cells and hemosiderin pigment. In the lumen there is a small fibrin clot enmeshing red blood cells, but no platelets.

On opening the heart, a perforation, measuring 0.5 cm. in diameter was found in the interventricular septum, communicating with the tear in the left ventricular wall. The cut surface of the muscle revealed no gross evidence of old or recent infarct; the muscle was uniformly brownish red, and, near the perforation, it was soft. The coronary arteries were everywhere patent, revealing little arteriosclerotic changes with the exception of the anterior descending branch of the left coronary artery; in this vessel, beginning 2.5 cm. from its origin and extending for 1 cm., there was a thick arteriosclerotic patch and a thrombus which together occluded the lumen. Microscopic examination of this region revealed evidence of old and recent hemorrhage into the arteriosclerotic plaque; large foam cells, free red blood cells, and hemosiderin pigment; marked atrophy of the media and a defect in the arterial wall whose edges were turned outward, very strongly suggestive of rupture (a "blow-out") (Fig. 5). A small fibrin clot enmeshing red cells, but revealing no platelets, appeared attached to the intima of the artery. Serial sections revealed marked stenosis of the artery by arteriosclerotic plaques, but the arterial wall was intact, except in the one region described previously. Microscopic examination of the myocardium revealed no evidence of recent or old myocardial in-

farction, but only infiltration of blood causing rupture and separation of muscle fibers in the vicinity of the myocardial tear (Fig. 6).

The evidence of recent and old hemorrhage into the arteriosclerotic plaques of the anterior descending branch of the left coronary artery indicates that the onset of cardiac pain on walking was due to reduction in the size of the arterial lumen in these regions. The terminal attack of pain was most likely due to rupture of the arterial wall and gradual tearing of the myocardium until the ventricular cavities communicated with the pericardial cavity, producing tamponade and sudden death.

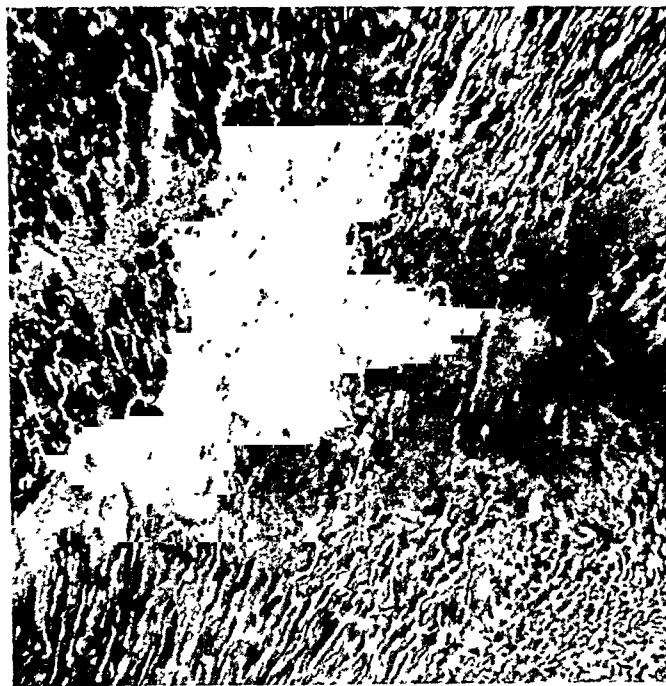


Fig. 6.—Case 4. Section of left ventricle at softened, hemorrhagic, ruptured area. Note well-preserved muscle and hemorrhagic areas disrupting muscle architecture. No muscle necrosis and no cellular inflammatory exudate.

DISCUSSION

Statistical analyses of the incidence of cardiac rupture reported by different authors vary considerably.²⁻⁷ The ideal pattern of facts should include the number of people in the community served by the medical observer or observers; the number of individuals older than 45 or 50 years and, therefore, candidates for coronary artery disease; the number of patients with symptoms or signs of coronary artery disease; the number with episodes of myocardial infarction; and, finally, an autopsy should be done on every case of death in the community in order to determine the number of cases with cardiac rupture. No such statistical analysis is to be found in the literature. Our own experience does not permit presenting such a pattern of facts. Three of the four cases of cardiac rupture belong to a group of about 12,000 patients (private, consultant, and hospital practice), of which about 1,000 had symptoms or signs of coronary artery disease. Four hundred fifty of these presented the clinical picture of myocardial infarction; there were 190 deaths and 49 autopsies. Thus, the clinician at the bedside would be justified in thinking of cardiac rupture in terms of three cases in 450 of myocardial infarction; whereas the pathologist about to perform the autopsy on a case of myocardial infarction would think of the incidence in terms of three in 49. The exact incidence cannot be determined without ideally collected statistics. In the light of present knowledge,

it appears justifiable to look upon myocardial rupture as a rare phenomenon, when thinking about the patient during the course of his illness. Between 70 and 80 per cent of all reported cases of cardiac rupture, were found in people over the age of 60 years. This statistical fact should be of some value in diagnosis and in estimating prognosis.

The conditions under which cardiac rupture occurred were mentioned in only 88 of the 632 cases collected by Krumbhaar and Crowell: eleven during violent conditions (severe overexertion, two; convulsions, three; trauma, three; and cardiac pain, three); 21 during sleep, and the remaining 56 during the mild activities or rest of everyday life. These statistics are inadequate to indicate the relationship of any particular form of exertion to cardiac rupture, but reveal the fact that absolute rest, as during sleep, does not prevent it. In three of our patients it occurred during absolute rest in bed; in the fourth it was initiated while the patient was seated on a streetcar.

The diagnosis of cardiac rupture was suggested in one of our four cases (Case 2), on what seemed to be direct evidence. There is no typical clinical picture or sign. Sudden development of cardiac pain, severe dyspnea, or shock within the first two weeks after the onset of myocardial infarction should suggest cardiac rupture. Paracentesis of the pericardium is a good critical test, which should eliminate or establish the diagnosis, when cardiac rupture is suspected. If there be a special type of murmur produced by the ejection of blood into the pericardium, then this has yet to be clearly described and differentiated from a pericardial friction rub or a valvular systolic murmur. In our case, the peculiar murmur could have been due to pericardial fibrin deposits; it did not resemble that reported by Reznikoff.⁹

Cardiac rupture usually occurs in the anterior ventricular wall, involving the thicker portions of the ventricle and not the apex, where the ventricular wall is thinnest. This suggests that intraventricular pressure does not play the dominant role in determining the difference between a myocardial infarct that does not rupture and one that does. On the other hand, the role of blood pressure was studied by Edmondson and Hoxie,⁵ who analyzed data in 72 cases of cardiac rupture in a group of 865 cases of recent infarction, and concluded that patients with hypertension after the establishment of the infarct show a greater tendency to rupture than those who have a low blood pressure. However, all three of our cases with myocardial infarction had a low or normal blood pressure. This experience leads us to believe that the particular site at which tearing is initiated is of greater importance than intracardiac pressure in determining cardiac rupture. If one assumes that a high blood pressure in the presence of a myocardial infarct is a significant determining factor, then one must explain the absence of rupture in patients who do show marked hypertension for many hours or days after the infarct develops, and in those who ignore their symptoms and continue performing heavy work. The observations made by Lowe⁸ on the muscle bundles of the heart suggest that rupture depends upon the point at which tearing is initiated. It is very likely that tears of the myocardium occur in most cases of infarction, but continuation of the tearing process until the entire thickness of the wall is involved must depend upon the plane in which it is initiated.

CONCLUSIONS

Four cases of ventricular rupture have been described. Three were through the left ventricle and occurred within the first six days after coronary artery occlusion and myocardial infarction, while the patients were at rest in bed;

these three cases had normal or low blood pressures; the fourth appears to have followed rupture of the anterior descending branch of the left coronary artery. Cardiac rupture occurs relatively rarely. The determining factor is probably the plane of myocardial muscle in which tearing is initiated. Absolute rest does not prevent cardiac rupture. The clinical diagnosis mainly depends upon pericardial paracentesis, when the condition of cardiac rupture is suspected. The general policy of treatment of coronary disease with myocardial infarction should not be determined by the fear of cardiac rupture, but rather by the probability that it will not occur.

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INTERVENTRICULAR SEPTAL DEFECT (ROGER'S DISEASE) OCCURRING IN A MOTHER AND HER SIX-MONTH FETUS

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THE present communication is the report of identical congenital cardiac lesions occurring in a 20-year-old mother and in her 6-month fetus. In each instance the lesion was a defect in the interventricular wall (Roger's disease) occurring at the base of the heart in the so-called "undefended space." This lesion was diagnosed during life in the mother and proved by autopsy, while the lesion in the infant was also demonstrated at autopsy.

It is generally stated that the etiology of most cases of congenital heart disease is unknown. Heredity has often been mentioned as a possible factor, although few cases have been described as occurring in parent and offspring or in siblings. Vierordt¹ quotes Potocki, who described the case of a man, aged 29 years, who had pulmonary stenosis and an interatrial septal defect and whose mother had congenital heart disease of an undetermined type. Vierordt also

gives a series, reported by Rezek, of eight cases of heart disease, in two instances congenital, occurring in four generations of a family. Walker² describes the case of a father, aged 48 years, and son, aged 18 years, each of whom had the classical signs of coarctation of the aorta.

Abbott,³ in a study of 850 cases of congenital heart disease, found that a history of congenital heart disease in the ancestry was much less common than was one of cardiac defect or other anomaly in other members of the same generation. In this series there was a history of congenital defect in a sibling in eleven cases. De la Camp⁴ described a family in which six children suffered from patent ductus arteriosus, and Gurlee⁵ referred to Kushoff's report of another family in which there were similar cardiac defects in six children in the same family. Smith⁶ described patent ductus arteriosus in each of identical twins as demonstrated at autopsy and commented on an account by Pezzi and Carugati⁷ of adult identical twins, both of whom had dextrocardia. Ellis⁸ examined two sisters, aged 9 years, 6 months, and 5 years, 3 months, in whom the diagnosis of patent ductus arteriosus was made on the basis of the clinical signs, while Stern⁹ described dextrocardia as occurring in brothers.

Further suggestive evidence that certain cases of congenital heart disease are due to inherent defects in the germ plasm is the not uncommon association of other congenital defects with congenital cardiac abnormalities. For example, in Vierordt's series of 700 cases of congenital heart disease there were 80 cases with associated anomalies, while in Abbott's¹⁰ series of 1,000 cases, 188 had associated anomalies elsewhere in the body.

It is quite possible that the paucity of reports of congenital heart disease occurring in succeeding generations is due to the fact that relatively few individuals suffering from congenital heart disease reach an age at which reproduction normally occurs.

CASE REPORT

The patient, J. K. (B.C.H. No. 1,002,175), a 20-year-old white woman, para 1, entered the hospital on Oct. 22, 1940, complaining that she had fainted without warning.

The patient stated that at the age of 4½ years she was seen at the Boston Children's Hospital because of bilateral congenital inguinal hernias. The hospital record indicates that the patient was slightly cyanotic and dyspneic at that time. On physical examination she was poorly developed and undernourished. The heart was slightly enlarged to the left and to the right. A systolic murmur was heard with the point of maximum intensity at the left border of the sternum just below the level of the third rib. A systolic thrill was palpable in this same area. The liver was slightly enlarged. There was no clubbing of the fingers. There were bilateral inguinal hernias. Because of the cardiac findings it was felt advisable to postpone surgical repair of the hernias. A diagnosis of patent interventricular septum was made, and the parents were advised to restrict the patient's activity.

Eleven years later (1936) the patient was seen at the Boston City Hospital because of discomfort from the hernias. It was felt her cardiac status at this time was such that she could undergo an operation, and the hernias were repaired without cardiac or other postoperative complications.

The patient continued to be cyanotic upon occasion, and the cyanosis was always aggravated by exercise and cold weather. She had an occasional nosebleed but never noticed any edema of the legs or ankles or dyspnea, and she did not find it necessary to restrict her activity.

At the time of admission she said that she was six months pregnant. She had suffered from attacks of intense cyanosis and extreme dyspnea since the onset of gestation. These attacks were more frequent and more severe as her pregnancy progressed. The first episode of syncope occurred on the day of admission, and this so alarmed her that she sought immediate hospitalization.

The past history was of interest in that the patient had frequent attacks of bronchitis as a child. The family history, as far as could be determined, was entirely free from cardiac disorders.

Physical Examination.—The patient was a normally developed, well-nourished, white woman in respiratory distress. Her skin was moderately cyanotic, and this was most marked about the face and extremities. There was moderate clubbing of the fingers. There were a few basal inspiratory râles heard over the posterior lung fields. Auscultation of the heart revealed a gallop rhythm and a loud systolic murmur over the upper third of the precordium, with the point of maximum intensity along the left border of the sternum at the level of the third rib. There was a palpable thrill over this area. The blood pressure was 120/70. An abdominal mass arising in the pelvis and extending to the umbilicus was felt. No fetal heart sounds could be heard.

Hospital Course.—Despite oxygen therapy the patient remained dyspneic throughout the day of admission and complained of feeling very ill and of having severe pain in the right shoulder. Suddenly, during the night, her color changed from a deep cyanotic purple to a pallid blue; the patient failed to respond to emergency stimulants and expired.

Laboratory Findings.—The hemoglobin was 95 per cent (Salhi); the red blood cell count, 5,300,000; and the white blood cell count, 7,500. The differential count and smear were considered normal. The urine was negative.

Autopsy (A40-860).—The body was that of a normally developed, well-nourished, 100-pound woman. There was moderately diffuse purplish discoloration of the face, hands, and lower extremities. There was slight clubbing of the fingers. There was no peripheral edema. The breasts were hypertrophied and were consistent with mid-gestation. There were old healed right and left inguinal operative scars. The abdomen was enlarged by a midline mass which extended to the umbilicus, and when the peritoneal cavity was opened this mass was found to be the uterus, extending 25 cm. above the symphysis. The liver was 8 cm. below the tip of the xiphoid process of the sternum. In each pleural cavity there were 300 c.c. of clear, yellow fluid. The pericardial cavity was essentially negative.

The heart weighed 500 grams. All chambers were dilated. The epicardium was smooth and glistening. The wall of the right ventricle was markedly hypertrophied. A defect measuring 2 cm. in diameter was present in the superior anterior portion of the interventricular septum. In the left ventricle the opening presented beneath the left posterior and anterior cusps of the aortic valve in the fibrous or so-called undefended space (Fig. 1). The upper margin of the defect reached to the base of the aortic cusps. In the right ventricle, the defect presented beneath the medial cusp of the tricuspid valve, the upper margin of the defect extending 0.3 cm. above the free edge of the valve leaflet. The endocardium of the right ventricle over the area opposite the defect was thickened and opaque. The valves were not remarkable. The coronary arteries were thin walled and patent. The ductus arteriosus was represented by a narrow fibrous strand, 0.2 cm. in diameter, and was totally occluded. The foramen ovale in the intraauricular septum had a 0.3 cm. patency anatomically but was considered to be functionally closed. The cardiac measurements were:

Tricuspid valve	13.0 cm.
Pulmonary valve	7.5 cm.
Mitral valve	12.0 cm.
Aortic valve	8.0 cm.
Left ventricle	1.1 to 1.5 cm.
Right ventricle	0.8 to 1.0 cm.

The right lung weighed 540 grams, and the left, 440 grams. Both lungs were similar and were dark red, boggy, and subcrepitant throughout. When cut, the parenchyma was extremely dark red in color and bloody; frothy material was expressed upon pressure. The trachea and main bronchi contained a small amount of mucoid material. The pulmonary arteries and veins were not remarkable.

A 3-cm. Meckel's diverticulum was found 90 cm. from the ileocecal valve. The remainder of the gastrointestinal tract was negative.

The liver weighed 1,720 grams. The organ cut with usual resistance, and the parenchyma was red brown with moderate accentuation of lobular markings.

The kidneys weighed 250 grams, combined. The capsules stripped readily leaving a red-brown surface which was smooth except for several depressed scars on both kidneys, with a deeper red brown, coarsely granular base. On section the kidneys presented a slightly narrowed cortex, 0.4 cm. in width. The cortico-medullary markings were distinct. The pelves and ureters were negative.

The adrenal glands were negative.

The genital organs were consistent with the date of the gestation. There was 1.5-cm. corpus luteum in the right ovary. The other ovary and tubes were not remarkable. The uterus measured 30 by 20 by 20 centimeters. Its wall was 0.8 cm. in thickness. The organ contained a female fetus, 31 cm. from crown to heel. The placenta was 15 cm. in diameter and attached to the posterior wall of the uterus. The placenta and membranes were negative.

Microscopic Examination.—Sections of the maternal heart were not remarkable except that the endocardium over the area in the right ventricle opposite the septal defect showed moderate fibrosis.

Sections of the lung showed a small amount of serum precipitate and some pigment-laden macrophages in the alveoli. There was clublike dilatation of the intra-alveolar capillaries with marked engorgement and widening of the capillary bed. In other focal areas there were sections of alveolar wall that were avascular and fibrous and thickened to approximately twice the usual width.

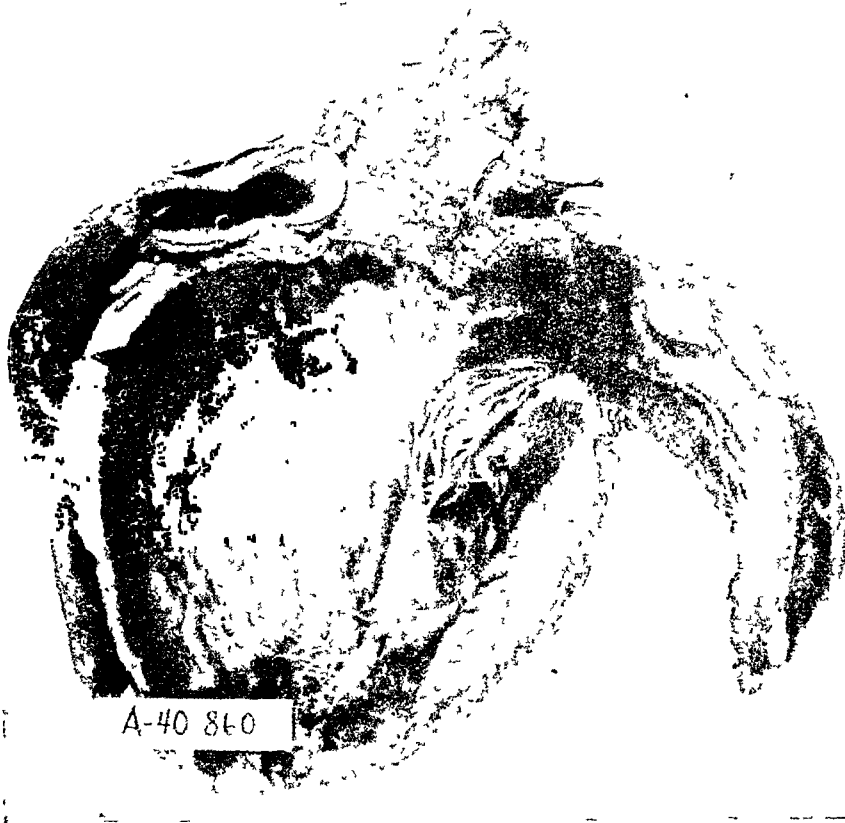


Fig. 1.—Gross photograph of the mother's heart illustrating the interventricular septal defect.

There was extreme hyperplasia of the walls of some arterioles with vascularization of the outer layers of the wall, and fibrin and polymorphonuclear leucocytes present directly beneath the intima. Other arterioles showed less acute reaction with lymphocytes, fibrosis, and marked narrowing of the lumina. The large pulmonary arteries showed no evidence of atherosclerosis.

The liver, aside from a moderate amount of central vein congestion, was not remarkable.

The kidneys were similar in microscopic appearance. The parenchyma was normal throughout, except for the areas subjacent to the scars, described on gross examination. These areas showed vascularized fibrous tissue with infiltration of lymphocytes and atrophic tubules. The glomeruli in these areas were reduced in number and showed some fibrosis. There were no significant vascular changes in the kidney.

The vertebral marrow showed a suggestion of hyperplasia of the red series, but this was not marked, and the other marrow elements were present in approximately the normal proportion.

In the breast the usual proliferation of acinar elements seen in pregnancy was present. It was not otherwise remarkable.

The usual changes of pregnancy were found in the uterus and sections of decidua and membranes were negative.

The remainder of the organs were not remarkable.

The Fetus.—The fetus weighed 640 grams and measured 31 cm. in length from crown to heel. (Nauwerck, in 1921, gave 434 grams in weight and 28 to 34 cm. in length as average for a six-month fetus.) There was very little vernixcaseosa and a moderate amount of lanugo hair. The skin was bright red and wrinkled about the head.

The fetal heart weighed 4.5 grams. There was a 0.4-cm. interventricular septal defect corresponding exactly, in position and relationships, to the defect described previously in the maternal heart. All other structures of the heart were normally developed and consistent with the age of the fetus.

The fetal organ weights were:

	Grams
Right lung	6.5
Left lung	5.0
Heart	4.5
Spleen	1.9
Liver	34.0
Kidneys (combined)	5.0

Microscopic Examination.—The lung of the fetus showed fetal type of alveolar formation with some lumen development. There was eosinophilic debris in a few of these lumina. There was no evidence of any inflammatory process anywhere in the sections or involving any of the blood vessels.

DISCUSSION

Embryologists have demonstrated that the subdivisions of the heart are completed in that period of development extending from the fifth to the eighth week of fetal life, during which time the embryo grows from 10 to 20 mm. in size (vertex to breech). It is at the end of this period that the closure of the foramen interventriculare takes place. The point of union of the aortic with the interventricular septum just below the adjacent ends of the anterior and left posterior aortic cusps remains transparent and free of muscle throughout post-partum life and is known as the pars membranacea septi or undefended space. The foramen ovale is not closed until post-partum. By the eighth week the valvular apparatus has almost completely developed. During the period from the eighth week of fetal life until birth, the portions of the heart that have been delineated undergo further development, but no marked transformation of the constituent parts of the heart takes place. This statement also holds true for the histologic differentiation of these structures, if the valve apparatus is excepted.

It is evident from the above that the heart described in the present fetus represents a true malformation, since the interventricular septum is always completed by the eighth week of fetal life, while the present fetus was at least 24 weeks old, as demonstrated by the clinical history and by fetal weight and measurements.

A further point of interest rests in the confirmation in this case of the frequent observation that, coexistent with one congenital anomaly, others may also be present. For example, in 1,000 cases reviewed by Abbott in 1932, 188 had other congenital anomalies in conjunction with that residing in the heart. In this case, the bilateral congenital herniae and the Meckel's diverticulum were associated with congenital cardiac defect.

Roger's disease is considered to be the second commonest cardiac congenital anomaly. In Abbott's series of 1,000 cases of congenital cardiac anomalies, localized ventricular defects were found in 274 cases or 27.4 per cent. In these 274 cases, all except 17 of the ventricular defects were at the basal portion of the heart. However, only 50 of these cases were unassociated with other cardiac anomalies. In the two cases described here ventricular defect

was the only cardiac anomaly. It is interesting to note that in Abbott's series of 50 cases in which the septal defect was uncomplicated, the mean duration of life was only 14½ years.

The persistent cyanosis was of interest in this case as it was present throughout life. Ventricular defect is considered to belong to the "acyanotic" group of congenital heart disease, as the shunt in the heart is from the arterial to the venous side. The lesions in the small arteries and arterioles of the maternal lung are apparently of recent date and the type of change and etiology are obscure. It is doubtful that these pulmonary vascular lesions played a role in the production of the patient's lifelong cyanosis. It is interesting to note that no vascular lesions were present in the fetal lung.

SUMMARY

1. A case of interventricular septal defect coexistent in a mother and her six-month fetus is described. The diagnosis in each case was confirmed by autopsy.
2. This case suggests a hereditary influence as an etiological factor in the genesis of certain cases of congenital heart disease.

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THE EFFECTS OF AMYL NITRITE ON THE DOWNWARD T WAVE OF THE ELECTROCARDIOGRAM

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INTRODUCTION

THE inhalation of amyl nitrite often causes the downward T_1 of the electrocardiogram, which is often seen in cases of left ventricular enlargement, to become upright.¹⁻³ However, no satisfactory explanation has been presented for this interesting effect. Inasmuch as we had previously noted that deep inspiration can also cause the downward T_1 of the electrocardiogram to become upright,⁴ we thought it might be of value to ascertain the relationship between the electrocardiographic effects of amyl nitrite and those of inspiration. The results of this survey are presented below.

MATERIAL AND METHOD

We studied the effects of amyl nitrite inhalation in a group of twenty-five cases of hypertension, enlargement of the heart, and a downward T_1 . In twenty of these cases respiratory changes were also recorded.

Standard leads, and then, unipolar extremity leads (taken with the author's method of obtaining augmented unipolar extremity leads and with his indifferent electrode of zero potential⁵) were recorded with the patient either sitting or semirecumbent. As each lead was taken the patient was instructed to take a deep breath, hold it a second or so, and then exhale. The patient was then given a 5-minim ampule of amyl nitrite to inhale, while Lead I was being recorded. As soon as an increase of heart rate was noted, the series of standard and unipolar extremity leads were taken in rotation. This continued for three or four minutes until after the rate had returned to normal.

GENERAL RESULTS

In order to correlate the changes in the standard and unipolar extremity leads, the following is of value^{6,7}: Although each standard lead records the potential difference between the two extremities used, Lead I tends to resemble the left arm lead, and Lead III tends to resemble the left leg lead, especially if Leads II and III are similar.

Occasionally, auricular premature contractions or ventricular premature contractions were produced by the inhalation of amyl nitrite, although sinus tachycardia was the most common arrhythmia observed. Occasionally no changes in heart rate were observed. This was noted among patients whose hearts were very large. The QRS complex usually deviated toward right axis deviation.

T-WAVE CHANGES

In sixteen of our twenty-five cases, the downward T_1 (and the downward T of the left arm lead) became upright after amyl nitrite inhalation. The effect of respiration was also recorded in fourteen of these cases. In all of these, inspiration also caused the downward T wave to become upright (Figs. 1, 2,

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and 3). As a matter of fact, as shown in Figs. 1 and 2, the amyl nitrite caused changes which are practically identical with those due to deep inspiration. However, in these cases, the tachycardia present after amyl nitrite inhalation was not seen during inspiration. In Fig. 3 not only did the T of Lead I and of the left arm lead become upright after amyl nitrite, but there was also a reversal of polarity of T of the right arm lead from (+) to (-). Although inspiratory studies were done only in the left arm lead in this case, we have often observed this effect of inspiration in the right arm lead in other cases with a downward T_1 .⁴

In seven cases, amyl nitrite inhalation caused no significant changes in the T wave. The effect of inspiration was noted in five of these cases. Four of these also had no appreciable inspiratory changes in the T wave, and in one case the effects of respiration were somewhat different from those of amyl nitrite (Fig. 4).

In two cases, one of which is illustrated (Fig. 5), the T wave remained downward in Lead I and in the left arm lead, but in the left leg lead and in Lead III, T, which had been upright, tended to become, or became, inverted (Fig. 5). The effects of respiration, recorded only in the unipolar extremity leads in this case, were very similar to the changes due to amyl nitrite. It may be noted that we have frequently observed such changes in the left leg lead and in Lead III on inspiration in cases of left axis deviation, with or without a downward T_1 .⁴ Attention may also be directed to the marked changes which occurred in the left leg lead in this case, in contradistinction to the minimal changes observed in Leads II and III.

The effects of amyl nitrite on the T wave in all our cases disappeared within three or four minutes, and the T waves became downward again. The inspiratory changes, of course, regressed as soon as the patient exhaled, and reappeared again on inspiration.

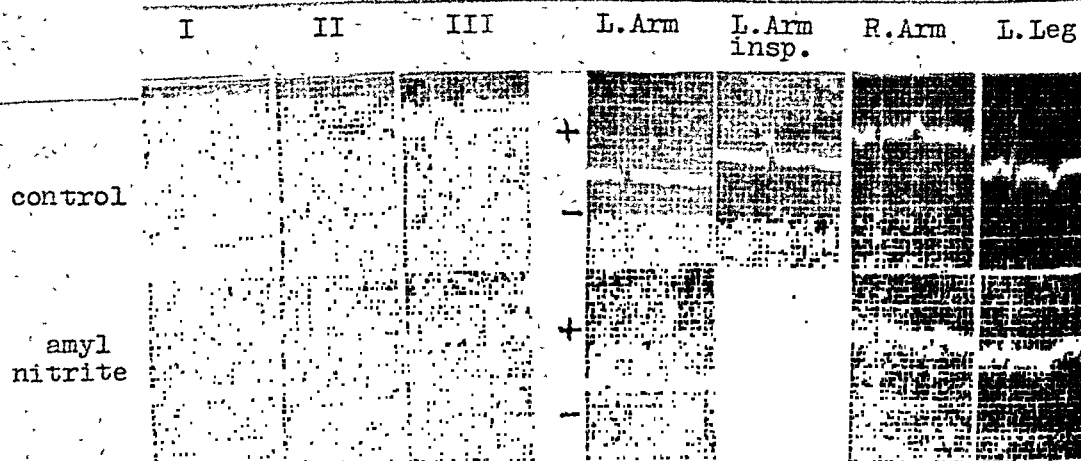
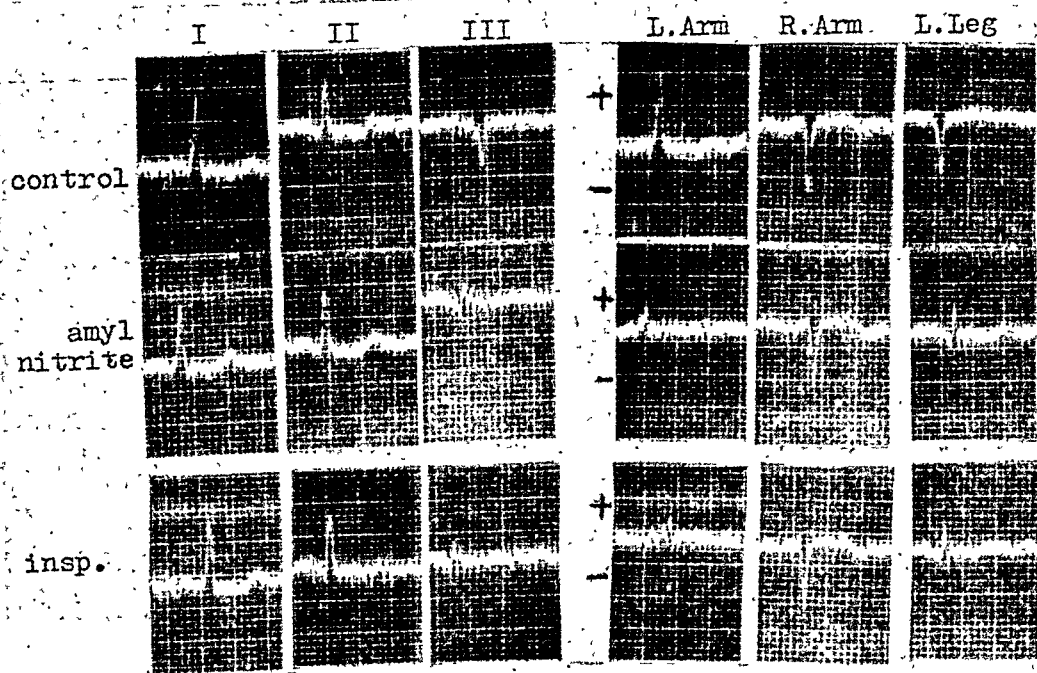
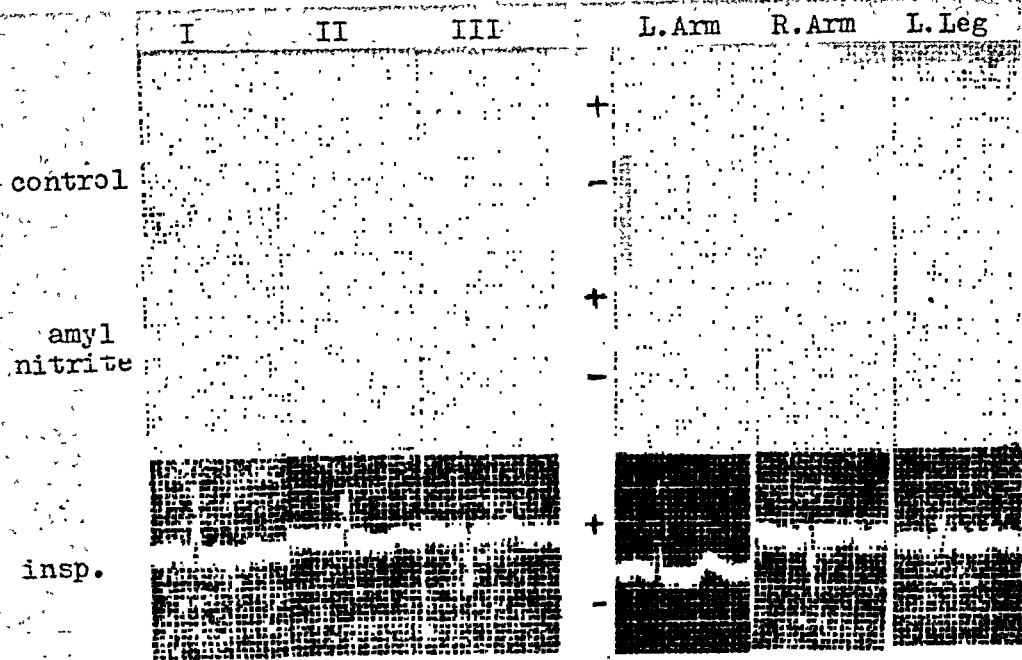
DISCUSSION

Most authors have ascribed the electrocardiographic changes after amyl nitrite inhalation to the fact that it increases coronary blood flow.¹⁻³ Actually, amyl nitrite not only does this, but also causes a fall in blood pressure, tachycardia, and a decrease in the size of the heart.⁹ It is, however, not necessary to explain the electrocardiographic deviations by means of these physiologic changes if we assume that the mechanism responsible for the electrocardiographic patterns seen on deep inspiration and after amyl nitrite inhalation is the same. It must be more than coincidence that, in eighteen of the twenty cases in which comparison between inspiratory and amyl nitrite effects were made, the electrocardiographic changes were practically identical.

It is well known that the effects of respiration on the electrocardiogram are due to rotation of the heart; the apex moves downward and the right ventricle tends to be more anterior (and the apex more posterior) on inspiration.⁸

Assuming that there is rotation of the heart after amyl nitrite inhalation, the mechanism of its production is probably a consequence of the decreased size of the heart. The smaller heart would tend to lie more vertically, and thus rotation (as described for inspiration) would take place. Another factor is the fact that hyperventilation was often observed by us after the amyl nitrite inhalation.

That the tachycardia is not of primary importance is shown by the fact that inspiration causes the same changes without the development of tachycardia. Furthermore, the T-wave changes have been shown to be unrelated to



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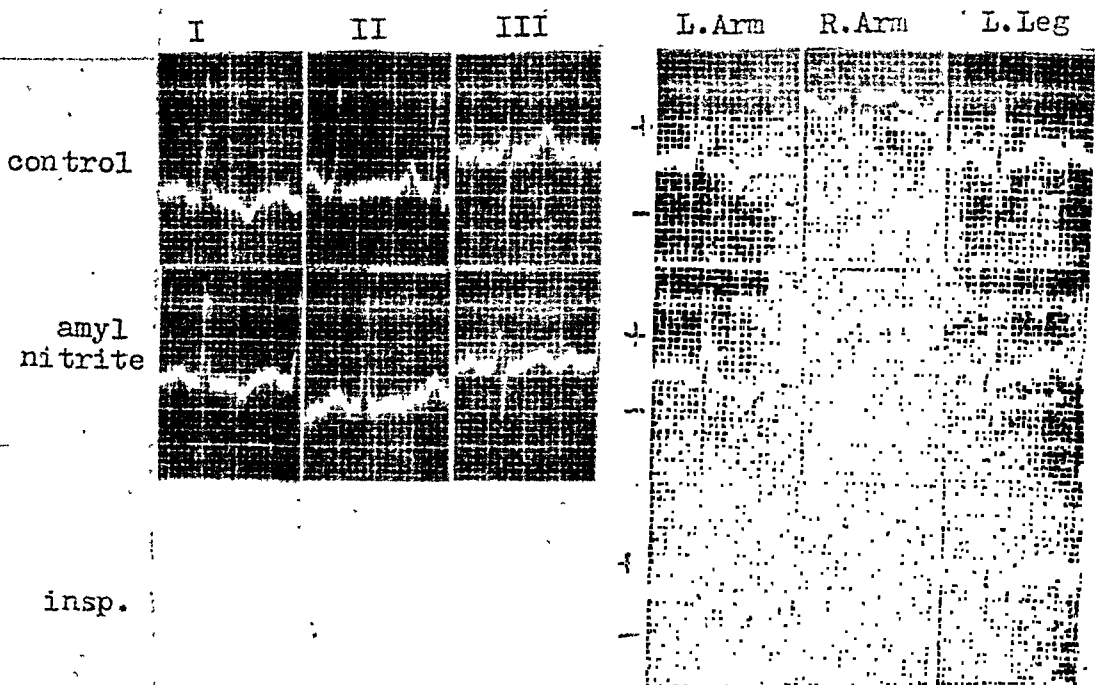
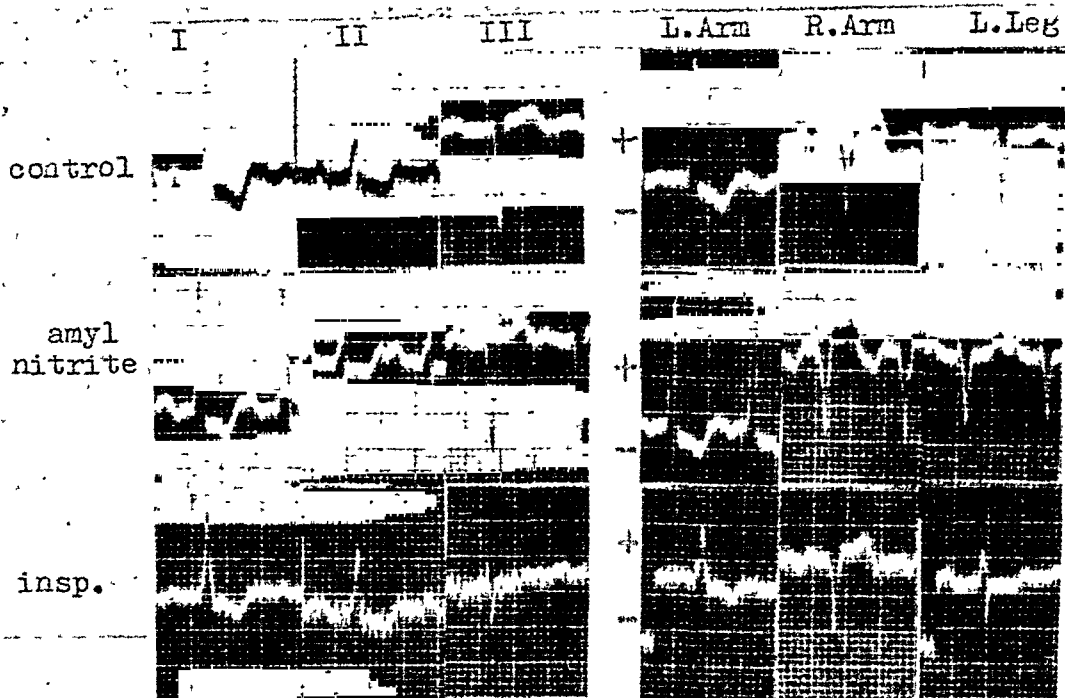


Fig. 4.—F.S., woman, aged 51 years. Hypertensive cardiovascular disease. Upper row, patient semirecumbent, breathing quietly. Middle row, patient semirecumbent, after inhalation of amyl nitrite. Lower row, patient semirecumbent, in deep inspiration.

Fig. 5.—V.B., woman, aged 47 years. Hypertensive cardiovascular disease, cardiac decompensation. Patient had been digitalized. Upper row, patient semirecumbent, breathing quietly. Middle row, patient semirecumbent, after inhalation of amyl nitrite.

Fig. 1.—F.A., man, aged 59 years. Hypertensive cardiovascular disease, cirrhosis of the liver and ascites. Upper row, patient sitting and breathing quietly. Middle row, patient sitting, after inhalation of amyl nitrite. Lower row, patient sitting, in deep inspiration.

Fig. 2.—B.K., woman, aged 75 years. Hypertensive cardiovascular disease. Upper row, patient sitting, breathing quietly. Middle row, patient sitting, after inhalation of amyl nitrite. Lower row, patient sitting, in deep inspiration.

Fig. 3.—F.L., woman, aged 39 years. Hypertensive cardiovascular disease. Upper row, patient lying, breathing quietly. The left arm lead marked "Insp." was taken during deep inspiration. Lower row, patient lying, after inhalation of amyl nitrite.

either the heart rate or blood pressure alterations, and may persist even after the heart rate and blood pressure have returned to normal.¹ Although there is no question that amyl nitrite does augment coronary blood flow, the effects of respiration certainly cannot be ascribed to such changes.

A few words might be said about those cases in which amyl nitrite did not cause a reversal of the downward T_1 . We noted that this usually occurred when there was marked depression of the RS-T segment, in addition to a downward T_1 . In these cases, inspiration was likewise ineffectual in causing a reversal of the downward T wave. This statement, of course, does not answer the fundamental question as to why inspiration should cause a reversal of the downward T wave in one case, and not in another. However, discussion of this is outside the scope of this paper, and will be presented elsewhere.⁴

In the case illustrated in Fig. 4, the electrocardiograms before and after amyl nitrite inhalation are very similar, with the exception of the tachycardia, although inspiration did cause slight changes. It may therefore be assumed that amyl nitrite caused no rotation of the heart in this case.

CONCLUSIONS

When amyl nitrite is inhaled it tends to cause a reversal of the downward T_1 (and the downward T of the left arm lead) which is often observed in cases of hypertension and left ventricular enlargement, and the T wave becomes upright.

These changes usually disappear within three or four minutes.

These changes are similar, if not identical, to those produced by deep inspiration. They can be explained by rotation of the heart, although other factors may take part.

When minor electrocardiographic changes occur, they are often much more marked in the unipolar extremity leads than in the standard leads.

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ADDENDUM

We have also observed that in normal subjects with vertical hearts and right axis deviation, both amyl nitrite and inhalation tend to make $T_{2,3}$ downward. Standing also does this. These changes are also due to rotation of the heart. In these cases, forward rotation of the apex around the transverse axis of the heart occurs in addition to the rotation described.

INCIDENCE OF EMBOLIC OR THROMBOTIC PROCESSES DURING THE IMMEDIATE CONVALESCENCE FROM ACUTE MYOCARDIAL INFARCTION

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THE following study was undertaken because of the desire to establish the incidence of embolic or thrombotic processes during the period of convalescence from acute infarction of the myocardium. These conditions include a second and distinct myocardial infarction, pulmonary embolism and infarction of the affected pulmonary tissue, cerebral vascular thrombosis or embolism, thrombophlebitis, and thrombosis or embolism of a peripheral artery. These phenomena, occurring during the convalescent period after coronary occlusion, frequently present serious therapeutic problems, and fairly frequently are responsible for the death of a patient whose recovery seems otherwise assured.

REVIEW OF THE LITERATURE

In any consideration of thrombosis and embolism subsequent to myocardial infarction, attention is directed to mural thrombi, either proved to be, or presumably, located in one or more chambers of the heart. That thrombi are frequently attached to the endocardium subjacent to a region of infarcted myocardium has been noted in many post-mortem studies. Among the earlier records are those of Wolff and White,¹ who stated that a mural thrombus almost always occurs in cases of myocardial infarction; yet in their series of twenty-three cases in which necropsy was performed, thrombi were mentioned in only seven (30 per cent). Levine and Brown² reported mural thrombi in thirty-eight (83 per cent) of forty-six cases in which necropsy was performed. Meakins and Eakin³ reviewed the protocols of sixty-two cases and found mural thrombi in twenty-nine (47 per cent). Bean's⁴ study of three hundred hearts in which there were infarcted regions revealed that 47 per cent of them had mural thrombi. Other authors⁵⁻⁹ have reported finding mural thrombi in from 17 per cent to 66 per cent of cases.

It is agreed that, prior to organization of thrombi, crumbling of the unattached portions loosens particles which may then be swept through the blood channels until they are arrested by the diminishing caliber of the arteries. In the absence of sufficient collateral circulation, infarction results. Since the left ventricle is involved in virtually all instances of myocardial infarction, thrombi occur predominantly in the left ventricle, and whatever emboli arise from such thrombi affect the systemic circulation. Because of the frequency with which portions of the interventricular septum are involved, both chambers are often found to contain mural thrombi. Emboli arising in the right ventricle of course lodge in the lungs.

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In 34 per cent of Bean's cases in which only the left ventricle contained thrombi, emboli were noted in the systemic arteries. He stated that embolism was unusually frequent when a thrombus was attached to the septum. Blumer¹⁰ noted clinically detectable emboli thirty-five times in twenty-seven of 175 cases. The lung was involved sixteen times, and probably in some instances its involvement was the result of emboli from systemic veins. Conner and Holt¹¹ studied data on 287 cases of coronary thrombosis and noted systemic embolic phenomena in twenty-eight instances.

Emboli arising in the chambers of the left side of the heart may lodge anywhere in the greater arterial tree, but, according to the foregoing studies, they are found most frequently in the spleen, kidneys, and brain. Less often, they affect the mesenteric vessels and the vessels of the extremities. The lodgement of large emboli on the bifurcation of the aorta has been the subject of some recent reports.^{12, 13}

A note of caution has been introduced by Blumer, who stated that it cannot be assumed that all arterial occlusions are of embolic origin, but that many must be the result of thrombosis occurring coincident with, or subsequent to, myocardial infarction.

Pulmonary embolism or thrombosis is frequently encountered among patients during the immediate convalescent period. Emboli may arise from mural thrombi of the right auricle or ventricle, or from thrombosis of the systemic veins. In Bean's experience, 75 per cent of the patients with right ventricular thrombi had pulmonary embolism. However, he stated that, in every instance in which massive pulmonary embolism had occurred and had caused death, the emboli had arisen from the veins of the pelvis or lower extremities. Among his three hundred cases, he noted a total of twenty-eight instances of pulmonary embolism, but there is no definite information as to the severity of this complication.

Meakins and Eakin reported pulmonary embolism in twenty-six of their sixty-two cases (42 per cent). This, too, was a study of post-mortem material, and complications are more frequent among patients who eventually die as the result of their illness than among those who recover. Conner and Holt, reporting on 287 cases, including patients who recovered, noted pulmonary embolism in twenty-one instances. Parkinson and Bedford⁸ found pulmonary emboli in eight of eighty-three cases in which necropsy was performed and in three of 100 cases ante mortem. Of Blumer's 175 cases, pulmonary emboli were detected clinically in sixteen instances.

Pulmonary embolism is a serious complication of coronary occlusion. Its reported incidence varies from 3 per cent in clinical series to 42 per cent in post-mortem series. It accounts for a relatively high percentage of deaths in the immediate convalescent period. In the series of sixty deaths reported by Woods and one of us (A. R. B.),¹⁴ pulmonary embolism was the cause in six instances. Master, Dack, and Jaffe,⁷ in reporting seventy-nine deaths, indicated that nine (11 per cent) were the result of pulmonary embolism. Five per cent of the three hundred patients in Bean's series died of pulmonary embolism.

Much attention has been directed to those cases in which pulmonary embolism occurs postoperatively among surgical patients. Thus, Priestley and Barker¹⁵ found it complicating surgical procedures in 0.52 per cent of the surgical cases. In 0.20 per cent, it was the cause of death. Splenectomy was the operation most frequently followed by pulmonary embolism; the incidence was 3.32 per cent. Embolism caused death in 0.77 per cent of cases, however. In

instances of laparotomy in which surgical procedures were done on the female pelvic organs, embolism occurred in 3.1 per cent of cases. In analyzing deaths occurring in the postoperative period, Priestley and Barker found that pulmonary embolism was the cause of death in 6 per cent of cases. Among 2,381 postoperative deaths in McCartney's¹⁶ series, pulmonary embolism accounted for death in 5.1 per cent of cases.¹⁷ Henderson¹⁸ noted that pulmonary embolism was the cause of death in 6 per cent of his series of surgical deaths during a period of ten years.

On the other hand, Belt¹⁹ reported data on fifty-six cases of pulmonary embolism, forty of which were medical cases and sixteen surgical cases. In 25 per cent of the fifty-six cases the patient had heart disease. Hines and Hunt,²⁰ in studying 234 cases of death from heart disease, found pulmonary infarcts in 34 per cent. The majority of patients had congestive heart failure. Thus it would seem proper to devote more attention to pulmonary embolism in medical cases, particularly in those in which the heart is diseased.

The literature contains few references to the occurrence of a second myocardial infarction during immediate convalescence from a previous infarction. Blumgart, Schlesinger, and Zoll²¹ reported data on two cases in which fresh thrombi were found in the coronary arteries, and in which the patients had suffered recent acute myocardial infarction. Both patients were in a state of shock and one had congestive failure. Most of the reports concerning complications of coronary occlusion do not mention a second attack during the immediate convalescent period.

Thrombophlebitis is frequently mentioned as complicating coronary thrombosis. Harrington and Wright²² noted it in five of 148 cases, and thought it added gravity to the prognosis. It was present in nine (15 per cent) of Meakins and Eakin's³ sixty-two cases in which necropsy was performed. Conner and Holt¹¹ reported venous thrombosis in four of their 287 cases.

Among factors influencing the occurrence of thrombophlebitis are reduction of blood pressure and rest in bed. These conditions reduce venous blood flow. Fall of blood pressure is one of the cardinal signs of myocardial infarction, and the lower level has been shown to be maintained for several weeks. During this period, patients are confined to bed and usually are cautioned to be as quiet as possible. Thus the venous blood is denied the impetus usually imparted by contractions of the skeletal muscles and by frequent changes of position. It would seem that patients confined to bed after coronary occlusion would show a high incidence of venous thrombosis or thrombophlebitis.

Barker and his associates²³⁻²⁶ correlated the incidence of thrombophlebitis and pulmonary embolism as they occur postoperatively, and found that in 16 per cent of their cases of thrombophlebitis pulmonary embolism occurred, and that in 6 per cent the embolism was fatal. They and others have pointed out the difficulty of detecting clinically the presence of thrombophlebitis, and the true incidence is believed to be higher than is generally recognized.

SELECTION OF CASES

For this study there were chosen one hundred consecutive cases of coronary occlusion encountered at the Mayo Clinic from January, 1940, to May, 1943, inclusive. The criteria for diagnosis included an attack of severe substernal pain, accompanied by sweating, pallor, and fall of blood pressure, and sometimes by collapse. In all instances, positive electrocardiographic evidence was present. In those instances in which death occurred during the period of ob-

servation and necropsy was performed, the clinical diagnosis was substantiated by the morphologic observations. Furthermore, only patients were selected who had entered one of the hospitals in Rochester, Minnesota, within a few days of the acute attack and had remained for a period of at least two weeks, unless death occurred prior to the conclusion of that period. In no case were anticoagulants used. Eighty-two of the patients were residents of Rochester or lived within a 25 mile (40 kilom.) radius of the city, an area for which the Clinic is the natural medical center. The remaining eighteen lived in more distant places, but they adequately fulfilled the other criteria for acceptance. A special effort was made to exclude cases in which there was the slightest suggestion that the patients might have come to the Clinic because of the severity of the original attack or because of the development of complications. In the cases accepted, complications occurred among 36 per cent of the eighty-two local residents, and among 38 per cent of the nonlocal residents. We believe that the cases represent an average group of patients similar to those seen in any city of comparable size located in a predominantly rural sector.

After the cases had been selected, the clinical records were examined carefully for evidences of complications involving the vascular system. Rigid criteria for the actual occurrence of a complication were established. In those instances (eleven) in which death occurred and necropsy was performed, the protocols of the post-mortem examination were reviewed. In addition, the hearts were examined to verify the presence of myocardial infarction. In two cases of death, necropsy was not performed. In those instances (eighty-seven) in which the patients recovered and were dismissed from the hospital, the following requirements for diagnosis of a vascular complication were set:

1. *Subsequent Myocardial Infarction*.—The diagnosis indicated, that a second and distinct myocardial infarction occurred while the patient was in bed in the hospital convalescing from the original attack. Such a diagnosis was made only after the occurrence of prolonged and typical pain, accompanied by a fall of blood pressure, characteristic fever, leucocytosis, and increased sedimentation rate, and by definite electrocardiographic evidence of a second infarction.

2. *Pulmonary Embolism*.—A diagnosis of pulmonary embolism was made when patients experienced a sudden, sharp pain in the thorax, with dyspnea and the development of a pleural friction rub, hemoptysis, and slight fever. In those instances in which roentgenograms were taken, there was positive evidence of infarction.

3. *Cerebral Embolism or Thrombosis*.—When sudden hemiplegia developed, a diagnosis of embolism or thrombosis of a cerebral vessel was made.

4. *Arterial Occlusion*.—This condition was recognized when signs of arterial insufficiency of an extremity developed suddenly.

5. *Thrombophlebitis*.—Such a diagnosis was considered when there were signs of local venous obstruction and inflammation. When deep veins were affected, there were pain and tenderness along the course of the veins, together with swelling of the extremity involved. In those instances in which superficial veins were involved, the thrombosed veins could be palpated and there were local pain, redness, and heat.

SEX AND AGE

Seventy-six of the patients were men, and twenty-four were women. The average age of the male patients was 57.9 years, that of the female patients

was 61.9 years, and that of the entire group was 58.8 years. The youngest patient was thirty-nine years of age, and the oldest patient was eighty-three years old. Table I indicates the ages by decades.

The sex and age distribution of the patients in this series corresponds closely to that in other series of patients suffering from coronary occlusion and myocardial infarction.

PERIOD OF OBSERVATION

Fourteen of the patients were in bed in a hospital when the occlusion occurred. In seven cases the occlusion occurred postoperatively, but in the other seven cases no operation had been performed. In the postoperative group, five patients were convalescing from transurethral resection and two from an operation on the stomach. Of the cases in which no operation had been performed, two patients had mild congestive heart failure, one patient was hypertensive, one had carcinoma of the bladder, one had carcinoma of the larynx, one was undergoing treatment for malnutrition, and one had been hospitalized because of symptoms of impending occlusion.

Of the remaining eighty-six, fifty-one entered the hospital within twenty-four hours of the time of occlusion, five entered during the second twenty-four hours, and thirty entered an average of eight days after the acute occlusion.

BLOOD PRESSURE

Forty-two patients were known by Clinic records to have had antecedent hypertension. Patients were considered to be hypertensive when the blood pressure exceeded 150/100, and when examination of the ocular fundi revealed arteriolar changes associated with chronic hypertension according to the criteria of Wagener and Keith.²⁷

Similarly, forty-six patients were known by Clinic records to have normal blood pressure. In twelve cases, no definite information concerning the blood pressure prior to myocardial infarction was available.

TABLE I. AGE OF PATIENTS BY DECADES

AGE (YR.)	PATIENTS
30 to 39	2
40 to 49	19
50 to 59	29
60 to 69	33
70 to 79	15
80 to 89	2
Total	100

PREVIOUS CORONARY DISEASE

Forty-three per cent of the patients gave a history of angina pectoris for periods varying from one month to sixteen years. The average duration of angina had been two years and nine months. Of this group, twenty-one patients were hypertensive. They had had angina an average of three years and ten months prior to their infarction. Sixteen of the patients who had had angina had had normal blood pressure, and the duration of angina had been two years and two months before occlusion occurred. Six of the twelve patients whose antecedent blood pressure was unknown had had angina an average of two years prior to their myocardial infarction. Twelve of the entire group of patients had had one myocardial infarction prior to the one observed here. Three of these patients died during their stay in the hospital.

CONCURRENT DISEASES

Ten patients had diabetes mellitus. Two of them had vascular complications and one patient died. One patient had syphilis and had received treatment for tabes dorsalis. This patient died. One patient had carcinoma of the larynx and one had carcinoma of the urinary bladder. The remaining patients had no other significant disease.

LOCATION OF INFARCT

The position of the infarcts was ascertained by using the Q-T patterns according to the method of one of us (A. R. B.²⁸). Fifty-two per cent of the infarcts were thus found to be in the anterior apical portion of the left ventricle, and 41 per cent were found to be in the posterior basal portion. In 7 per cent of the cases, the electrocardiogram was thought to indicate acute infarction, but the locations were not definitely established. Six of these patients died, and, at necropsy in each case, acute infarctions were found in the interventricular septum.

VASCULAR COMPLICATIONS

Of the one hundred patients, 37 per cent suffered from complications of a thrombotic or embolic nature. Twenty-eight per cent of the total group had only one complication, whereas 9 per cent had multiple complications (Table II).

Fifteen patients had a second and distinct myocardial infarction. In twelve instances, the second infarction occurred during the fourth to the thirteenth day after the first infarction, whereas, in the remaining three cases, the second infarct occurred on the twentieth, twenty-ninth, and sixty-eighth day, respectively. Of the fifteen patients with multiple infarctions, ten had had normal blood pressure prior to their first infarction. Thus, 22 per cent of the patients who had had normal pressure prior to the first myocardial infarction had subsequent occlusion of a coronary vessel with consequent myocardial infarction. On the other hand, only 5 per cent of the hypertensive patients had subsequent coronary occlusion and myocardial infarction. Among the patients whose antecedent blood pressure was unknown, there occurred second infarctions in three instances (25 per cent). A second infarction caused the death of one of the patients, a 43-year-old man who had normal blood pressure.

Pulmonary embolism and infarction occurred fourteen times in the entire group; it affected seven patients who had hypertension and six patients who previously had had normal blood pressure, and occurred once among the twelve patients whose previous blood pressure was unknown. Pulmonary embolism was the cause of death in one instance. Embolism occurred on the fifth day in one case, but, in the remaining clinical instances of embolism and infarction, the embolism occurred during the sixteenth to the thirty-seventh day.

TABLE II. INCIDENCE OF VASCULAR COMPLICATIONS IN 100 CASES OF ACUTE MYOCARDIAL INFARCTION; TOTAL PATIENTS WITH COMPLICATIONS, THIRTY-SEVEN

COMPLICATIONS (MULTIPLE IN SOME CASES)	INCIDENCE
Second myocardial infarction	15
Pulmonary embolism	14
Cerebral vascular accident	8
Thrombophlebitis	7
Peripheral arterial occlusion	4
Total complications	48

TABLE III. COMPLICATIONS WITH RESPECT TO PATIENT'S PREVIOUS BLOOD PRESSURE

COMPLICATION	NO HYPERTENSION		HYPERTENSION	
	CASES	PER CENT	CASES	PER CENT
Second myocardial infarction	10	22	2	4
Pulmonary embolism	6	13	7	17
Cerebral vascular accidents	1	2	7	17
Thrombophlebitis	3	6	3	7
None	26	57	23	55
Total	46	100	42	100

Cerebral vascular accidents occurred in eight cases. However, among patients who had had antecedent normal blood pressure, they occurred only once (2 per cent), whereas, among patients who had had hypertension, they occurred seven times (17 per cent) and were the cause of death in two instances in the latter group. In both of these cases, necropsy revealed that the vascular occlusion was the result of intravascular thrombosis. This complication occurred during the tenth to the twentieth day in five cases, and on the fourth, seventh, and forty-first days in the remaining three cases.

The left femoral artery of one patient was suddenly occluded on the tenth day after myocardial infarction. This patient subsequently died from pulmonary embolism, and at necropsy no mural thrombus was found. In three other cases infarcts of the spleen or kidneys, or both, were found at necropsy.

Thrombophlebitis was a complicating factor among seven patients, three of whom had had hypertension and three others had had normal blood pressure prior to myocardial infarction. One patient whose blood pressure prior to myocardial infarction was unknown had thrombophlebitis. Five of the patients had subsequent pulmonary emboli and infarction, and an embolus was the cause of death of one of these patients.

Table III indicates the incidence of complications with respect to the level of the patient's blood pressure prior to myocardial infarction.

CONGESTIVE HEART FAILURE

Six patients who had had hypertension had congestive heart failure during at least a part of their hospital stay. Two of these patients had no complications. A third patient had a definite pulmonary embolus on the thirtieth day. The other three patients died, and, at necropsy, one was found to have thrombophlebitis of the systemic veins and multiple pulmonary infarcts. The second patient had mural thrombi in both ventricles and multiple pulmonary infarcts. The third patient had a friable, irregularly shaped embolus in the left pulmonary artery. There was no mural thrombus in this case. The source of the embolus was not ascertained.

Of the patients who had had antecedent normal blood pressure, two exhibited evidence of congestive heart failure. One patient died. At necropsy a right-sided pulmonary infarct and a nonfatal embolus in the left pulmonary artery were found. There was a mural thrombus in the left ventricle. The second patient had no complications. Congestive heart failure was present in one patient whose blood pressure before infarction was unknown. This patient had a pulmonary infarction on the twenty-sixth day.

DIGITALIS

Only twelve of the patients were given digitalis in therapeutic doses. Seven of these had varying degrees of congestive heart failure. In four instances, digitalis was given to patients because decompensation was thought to be im-

TABLE IV. VASCULAR COMPLICATIONS AMONG PATIENTS WHO RECEIVED DIGITALIS

CASE	HYPER-TENSION	CONGESTIVE HEART FAILURE	SUBSEQUENT INFARCTION	PULMONARY EMBOLISM	THROMBO- PHLEBITIS	ARTERIAL OCCLUSION	DEATH
3	Group 2	-	-	Present*	Present	Present	Yes
4	Group 1	Present	-	Present	Present	-	Yes†
5	Group 2	-	-	-	-	Present	Yes†
22	Group 1	-	-	-	-	-	No
23	Group 2	Present	-	Present	-	-	No
31	Group 1	Present	-	Present	-	Present	Yes
37	Group 3	Present	-	-	-	-	No
55	-	-	Present	Present	-	-	No
57	-	Present	-	Present	-	-	Yes†
58	-	Present	-	-	-	-	No
69	-	-	-	-	-	-	No
88	Unknown	Present	-	Present	-	-	No

*Fatal pulmonary embolus.

†Mural thrombus present in heart.

minent but had not yet developed. In one case, 6 c.c. of lanatoside-C (Cedilanid) were given to a patient who had auricular fibrillation. Pulmonary embolism and infarction occurred in five of the seven cases complicated by failure in which the patients received digitalis. Among the five patients who did not have congestive heart failure, three had vascular complications. Five of the twelve patients died. Pulmonary embolism was the cause of the death of one of these. Table IV shows the complications which occurred among the patients who received digitalis.

DEATHS

Thirteen of the 100 patients died during their stay in the hospital. In four cases vascular phenomena were the cause of death: two patients died of cerebral thrombosis, one of pulmonary embolism, and one of a second coronary occlusion. Seven patients died suddenly, and the mechanism of death was not known clinically. Five of these patients were examined post mortem. In four cases there were multiple pulmonary infarcts, and fresh thrombi were found in the pulmonary arteries. In the opinion of the pathologist, these were not the principal cause of death. Two patients died of myocardial failure.

Eleven of the thirteen patients who died were examined post mortem. In seven hearts there were mural thrombi in the left ventricle. Thrombi were

TABLE V. DEATHS

CASE	HYPER-TENSION	CONGESTIVE HEART FAILURE	SUBSEQUENT INFARCTION	PULMONARY EMBOLISM	THROMBO- PHLEBITIS	ARTERIAL OCCLUSION	CAUSE OF DEATH
1	Group 2	-	-	-	-	Cerebral	Congestive heart failure†
3	Group 2	-	-	Present	Present	Femoral	Pulmonary embolism
4	Group 1	Present	-	Present	Present	-	Sudden death*†
5	Group 2	-	-	-	-	Renal	Sudden death*†
8	Group 2	-	-	-	-	Cerebral	Cerebral thrombosis†
10	Group 2	-	-	-	-	Cerebral	Cerebral thrombosis
12	Group 2	Present	-	Present	-	-	Congestive heart failure†
18	Group 2	-	-	Present	-	-	Sudden death*†
31	Group 1	Present	-	Present	-	Renal	Sudden death*
47	-	-	-	-	-	Cerebral	Sudden death*
50	-	-	Present	-	-	-	Coronary occlusion
57	-	Present	-	Present	-	-	Sudden death*†
68	-	-	-	-	-	-	Sudden death*

*In these seven cases, death was sudden and the exact cause was unknown.

†Mural thrombi present.

present in both ventricles in two instances, and, in addition to left ventricular thrombi, auricular thrombi were noted in four instances. Data pertinent to these patients are summarized in Table V.

COMMENT

This series of one hundred cases is too small to allow one to make dogmatic statements concerning the statistical data accumulated. However, such data may be considered suggestive.

Of primary interest is the high (37) percentage of thrombotic or embolic complications. In four instances such complications were the cause of death, and in eight cases these complications were important contributing factors to the death of the patients. Of those patients who had complications and lived, the complicating factor probably had no serious consequences in eight instances. However, in seventeen cases the complications were of definite importance to the patient, for fourteen of them had subsequent myocardial infarction, with further diminution of cardiac reserve, and three other patients became permanent invalids because of hemiplegia following cerebral thrombosis or embolism.

Thus, we may say that complications of a vascular nature were of major importance in 78 per cent of the cases in which they occurred. If we consider the entire group of one hundred cases, important complications occurred in twenty-nine cases.

It is also interesting that, in those instances in which a second coronary occlusion and myocardial infarction occurred, ten of the patients had been known to have normal blood pressure prior to the occlusion, whereas only two had been hypertensive. If the second occlusion was of thrombotic origin, it is conceivable that an important precipitating factor could have been the fall of blood pressure after the original occlusion and infarction. Master, Jaffe, Dack, and Silver²⁹ noted that, in 57 per cent of 538 cases of coronary occlusion, there was a rapid fall of blood pressure, whereas, in 43 per cent, the fall was gradual, and the blood pressure attained the minimal value in one to three weeks. In the majority of their cases, the lowest pressures were reached between the twelfth and the twentieth day. Among persons with normal blood pressure, the systolic pressure fell to less than 100 mm. Hg in 71 per cent of the cases, whereas, among patients who had hypertension, the systolic pressure reached 100 mm. Hg in only 27 per cent of the cases.

From these data, one might postulate that further thromboses would be more likely to occur among persons with normal blood pressure than among hypertensive persons, and, in our cases of a second occlusion, we find such a relationship.

Pulmonary embolism was the cause of death of only one patient. However, it contributed considerably to the death of five other patients. In six cases, there were no apparent serious consequences of embolism. Thrombophlebitis was present in three cases of pulmonary embolism.

Six of the patients who suffered from pulmonary embolism died during their stay in the hospital. Necropsy was performed, and, in four cases, mural thrombi were found in the right auricle or ventricle. The percentage incidence of pulmonary embolism in this series is approximately the same as that reported by other authors in similar series of cases.

In considering cerebral thrombosis or embolism, it is probably significant that this accident occurred in 17 per cent of the patients who had hypertension, but in only 2 per cent of the nonhypertensive patients. In two of the eight

cases in which this complication occurred, the pathologic process was demonstrated by necropsy to be thrombosis. In Bean's cases, cerebral vascular accidents were embolic in six instances and thrombotic in nine instances. Here, too, the postinfarction fall of blood pressure may be a precipitating factor. An additional factor probably is local arterial disease, so commonly found in the cerebral vessels of hypertensive patients.

Factors contributing to thrombophlebitis or venous thrombosis of the extremities have been mentioned previously. For purposes of emphasis, we repeat that they include lowered systemic blood pressure, enforced rest in bed, and lack of movement of the extremities. Clinical investigations on patients who had myocardial insufficiency have indicated a reduced blood flow, and Smith and Allen³⁰ have reported that the venous circulation is significantly slowed in 82 per cent of cases after major surgical procedures. It may be expected that venous stasis is present in as high or higher percentage of patients who have myocardial infarction.

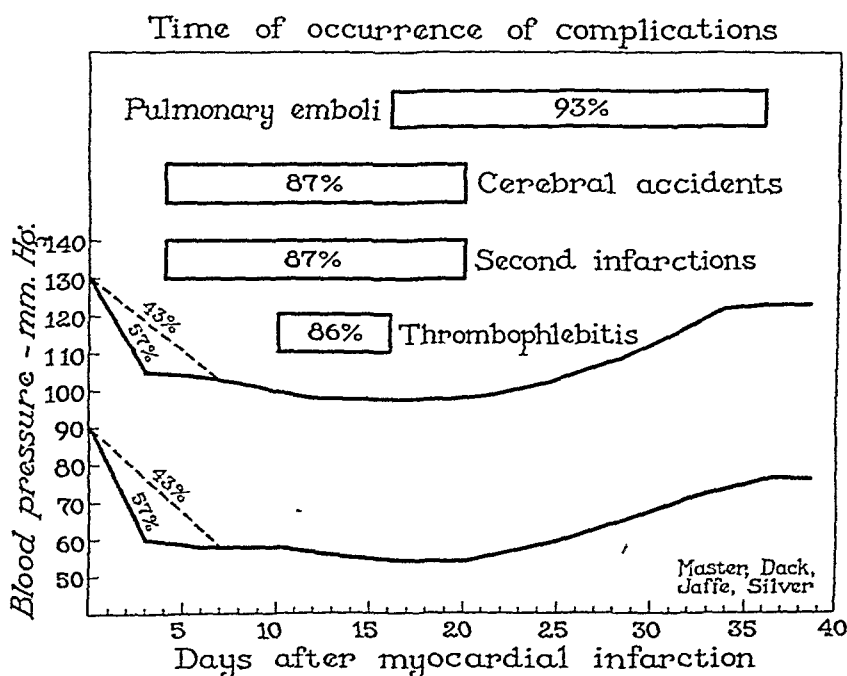


Fig. 1.—Time of occurrence of complications with respect to blood pressure. The paral-lelograms represent values explained in the paper. The curves are derived from a study by Master, Jaffe, Dack, and Silver.²⁹

We believe that it is important to comment on the time of occurrence of the complications which presumably involve thrombosis. Eighty-seven per cent of the instances of second myocardial infarction occurred between the fourth and the twentieth day. Eighty-seven per cent of the instances of cerebral vascular accidents occurred within the same period. Eighty-six per cent of the cases of thrombophlebitis were noted between the tenth and the sixteenth day. It is probably more than coincidence that the great majority of complications occurred during the time that the lowest levels of blood pressure were maintained. This relationship is illustrated in Fig. 1.

Because of the small number of patients who received digitalis, we can only comment with interest on the role of this drug in causing vascular complications. In assaying digitalis, Macht³¹ found that, during injection of tincture of digitalis into cats, the coagulation time was progressively shortened from six minutes to one minute and fifteen seconds. He noted a similar effect in assaying ouabain. When he heparinized the cats, he found that the amount of

tincture of digitalis required to cause the heart to stop was increased from 8.5 c.c. per kilogram to 10.2 c.c. per kilogram. This effect he thought was due to prolongation of the coagulation time. Macht concluded that, under certain pathologic conditions, digitalis promotes intravascular clotting and predisposes to thrombo-embolic accidents.

De Takats, Trump, and Gilbert³² presented data on four cases which they interpreted as illustrating the effect of digitalis on the clotting mechanism. Furthermore, they reported a diminished effect of heparin on both human beings and dogs in the presence of digitalization. In another article, de Takats³³ stated that, after cardiovascular accidents, patients show decreased tolerance to heparin.

Of our group of twelve patients who received digitalis, seven had pulmonary embolism and infarction, and another had multiple infarcts in the kidneys. Detectable thrombophlebitis was present in two cases. It must be remembered that seven of the patients had congestive heart failure, a condition which in itself fosters thrombosis.

Further study is necessary to define clearly the role of digitalis in thrombo-embolic phenomena among human beings.

SUMMARY

One hundred consecutive cases of acute coronary occlusion and myocardial infarction were studied, and the incidence of subsequent intravascular thrombosis or embolism during the immediate convalescent period has been tabulated.

Complications of a thrombotic or embolic nature occurred in thirty-seven cases. In four cases the complication caused the death of the patients, in eight cases the complications were contributing factors in the death of the patients, and in seventeen other cases the complication was of considerable importance in the future health of the persons concerned.

A second myocardial infarction occurred in fifteen cases, pulmonary embolism occurred in fourteen cases, cerebral thrombosis or embolism complicated eight cases, arterial occlusions were noted in four instances, and thrombophlebitis complicated seven cases.

Forty-six of the patients were known to have had normal blood pressure prior to the coronary occlusion and myocardial infarction. Ten (22 per cent) had subsequent myocardial infarctions during the immediate convalescent period. Forty-two of the total group of one hundred patients had had hypertension prior to coronary occlusion, and two (5 per cent) had subsequent myocardial infarctions during the immediate convalescent period. In twelve cases, the blood pressure prior to coronary occlusion was not definitely known. Three of these patients had a second myocardial infarction during their residence in the hospital.

Eighty-seven per cent of the cases of second myocardial infarction and 87 per cent of the instances of cerebral vascular accidents occurred between the fourth and the twentieth day, and 86 per cent of the cases of thrombophlebitis occurred between the tenth and the sixteenth day, periods when the blood pressure of patients who have acute myocardial infarctions has been demonstrated to be at the lowest levels.

Thirteen of the patients died. Two of them died as a result of cerebral thrombosis, one from pulmonary embolism, and one from a second myocardial infarction. Two other patients died of congestive heart failure. In seven instances death was sudden, but the exact cause was not ascertained.

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A CASE OF INFECTION WITH BRUCELLA SUIIS, CAUSING ENDOCARDITIS AND NEPHRITIS; DEATH FROM RUPTURE OF MYCOTIC ANEURYSM

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DESPITE the increasing frequency with which brucellosis is being recognized clinically, reports of anatomic studies made at autopsy are rare. In 1937, von Albertini and Lieberherr¹ collected from the literature, and supplemented from their own experience, reports of thirty-nine cases in which pathologic examination had been performed. Of these, fourteen lacked histologic studies and two were examined only by biopsy. The authors included eight cases of their own. It is obvious from their bibliography, however, that they did not review the English literature.

Forbus² states, "There are three fairly well-defined types of fatal brucellosis, namely (1) the septicemic or relatively acute form, (2) the focal or localized form of infection, again relatively acute, and (3) the chronic lymphogranulomatous type with prolonged course." In the second type must be included the rarely reported cases of *Brucella* endocarditis.

In 1897, Hughes³ reported three cases in which endocarditis was found as a complication of infection with what would now be termed *Brucella melitensis*. Scott and Saphir⁴ studied a patient with *Br. abortus* bacteriemia who was found at autopsy to have friable vegetations on scarred mitral and aortic valves. De La Chappelle⁵ reported the case of a patient whose blood culture was positive for *Br. melitensis* A. The aortic valve was found at autopsy to have fresh vegetations superimposed on old scarring. Casanova and d'Ignazio⁶ performed an autopsy on a patient and secured a pure culture of *Br. melitensis* from vegetations on the aortic valve. Ulcerative endocarditis was observed at autopsy by Gounelle and Warter⁷ in a patient whose blood culture contained *Br. melitensis*. Rennie and Young⁸ studied a patient whose blood contained *Br. abortus*. At autopsy, fresh vegetations were found on a scarred and stenotic mitral valve. In 1938, Levy and Singerman⁹ reported the case of a patient whose blood culture yielded *Br. melitensis*. At autopsy, friable vegetations were found on a scarred mitral valve. Smith and Curtis¹⁰ published studies on a patient whose blood cultures were positive for *Br. abortus*. At necropsy, there were ulcerative, thrombotic vegetations on the aortic valve. Patchy areas of calcification were found in the leaflets of the aortic cusps. The interauricular septum was the site of an ulcerated, aneurysmal dilatation. Spink and Nelson¹¹ studied a patient with brucellosis complicated by endocarditis. At autopsy, vegetations were found on a previously normal aortic valve. *Br. abortus* was obtained in pure culture from these vegetations. Wechsler and Gustafson¹² reported the occurrence of *Brucella* endocarditis on a bicuspid aortic valve. Spink, Titrud, and Kabler¹³ obtained a pure culture of *Br. abortus* from vegetations on the mitral valve of a patient who died of brucellosis. Scarring of the mitral and aortic valves and the presence of Aschoff bodies proved the prior

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existence of rheumatic endocarditis. Call, Baggenstoss, and Merritt¹⁴ have recently added reports of two cases in which infection with *Br. abortus* was proved by blood culture. In one, fresh vegetations were found on the aortic valve, and, in the other, on the mitral valve. In both cases there was evidence of pre-existing rheumatic endocarditis.

Involvement of the endothelium other than that of the heart by *Brucella* is apparently even more rare. Mycotic aneurysms of clinical importance have seldom been reported in brucellosis. Rupture of a mycotic aneurysm of the basilar artery was found by Hansmann and Schenken¹⁵ at autopsy on a patient whose cultures of blood and spinal fluid contained *Br. suis*. Knighton¹⁶ reported the case of a man with fever whose blood contained agglutinins against *Br. abortus* and *Br. melitensis* in a dilution of 1:100. A clinical diagnosis of *Brucella* endocarditis was made. A mycotic aneurysm, 6 by 8 cm., involving the right axillary and subclavian arteries, developed. Recovery of the patient was attributed to ligation of the aneurysm.

In their extensive studies on *Brucella* infections in Iowa, Hardy, Jordan, Borts, and Hardy¹⁷ concluded that, in general, *Br. suis* is more virulent for man than *Br. abortus*. From animal inoculation and clinical experience, it has been thought that the porcine strain was also more virulent than the caprine species, *Br. melitensis*. It is therefore remarkable that endocarditis has not hitherto been reported as a complication of infection with *Br. suis*. That the organism attacks endothelium is proved by the case of mycotic aneurysm reported by Hansmann and Schenken.¹⁵ Spink and Nelson¹¹ considered that in many of the cases reported as *Brucella* endocarditis the diagnosis was not proved. They demanded that such a diagnosis be substantiated by bacteriologic and anatomic evidence obtained at autopsy.

We will report studies on a patient with endocarditis and diffuse nephritis who died from rupture of a mycotic aneurysm. The significant lesions were proved to be due solely to *Br. suis*. The evidence presented meets the rigid criteria set up by Spink and Nelson. As far as we can ascertain, this is the first report of endocarditis proved to be caused by the porcine strain of *Brucella*.

CLINICAL OBSERVATIONS

M. K., a farmer, 45 years old, was admitted to the University Hospital Dec. 10, 1943, in semistupor. His wife said that, during September of that year, malaise and intermittent fever had gradually developed. He had performed his work on the farm, interrupting it with intervals of a few days in bed. After October 6, he had been in bed continuously. His wife had kept a daily record of his temperature; this is included in Fig. 1. During November, his attending physician had administered sulfanilamide for one week with no diminution of fever, or alleviation of symptoms. About December 1, his condition became noticeably worse. He had been alternately delirious and somnolent. An eruption had appeared on the skin, and the ankles had become swollen.

Upon admission to the hospital, examination revealed a well-developed and well-nourished man, 5 feet 4 inches (162.5 cm.) in height, weighing 149 pounds (67.7 kg.). He was stuporous and disoriented. There was some evidence of dehydration. Purpuric areas were present, particularly in the skin over the legs and feet, although there were a few on the upper part of the body. In addition, there was a faun-colored maculopapular eruption which was confluent over the thorax and abdomen. Edema over the ankles pitted to a depth of 5 millimeters. The accessible lymph nodes were not enlarged. There was no pallor, cyanosis, or dyspnea. The eyes appeared normal. The extraocular movements were normally performed. The pupils reacted to light and in accommodation. The ocular fundi contained no hemorrhages, edema, or areas of degeneration. The nose, ears, teeth, and tongue were negative. The neck was not remarkable. The heart was normal with respect to size, rate, and rhythm. The quality of the heart sounds was not altered. A soft, blowing, systolic murmur was heard over the entire precordium. The contour of the peripheral arterial pulse was normal.

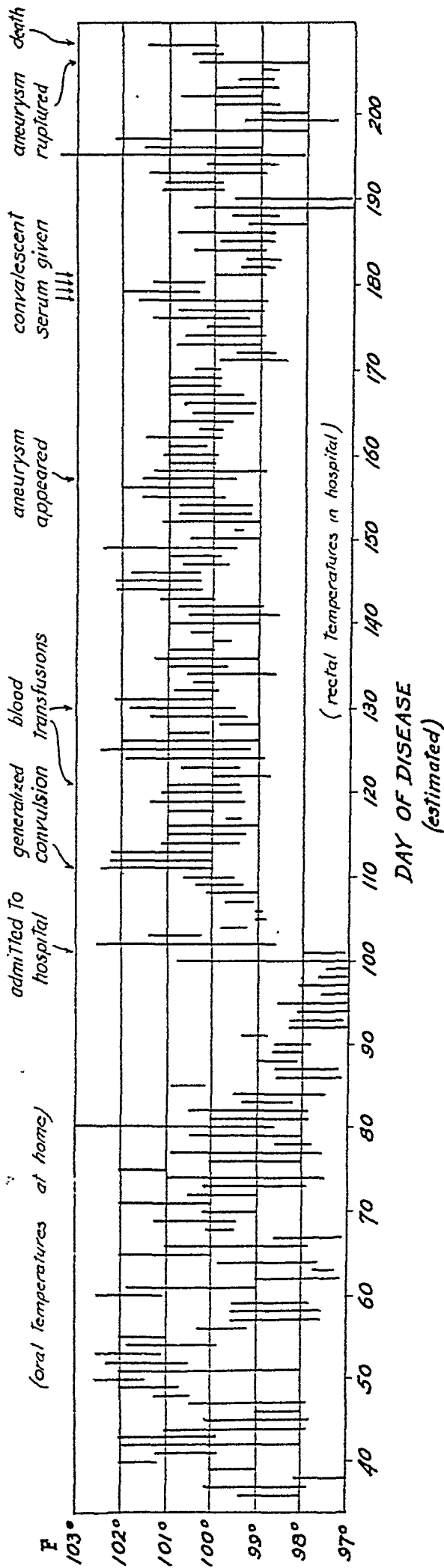


Fig. 1.—Record of daily temperature.

The blood pressure measured 150/82. The lungs were normal. There was some gaseous distention of the abdomen. The liver and spleen could not be palpated. There was no evidence of free fluid in the peritoneal cavity. The genitals and rectum were negative. The prostate was normal in size and consistency. The tendon reflexes were normal. There were no pareses.

The first specimen of urine to be examined was acid in reaction, with a specific gravity of 1.010. It contained no albumin or glucose, but the sediment included many erythrocytes and granular casts. The hemoglobin of the blood measured 10.5 Gm. per 100 c.c. (Haden-Hausser). The erythrocyte count was 2,950,000 per cubic millimeter. The leucocytes numbered 4,700 per cubic millimeter. The differential counts were normal.

A tentative clinical diagnosis of uremia was made. It was thought that the probable cause was focal embolic nephritis due to subacute bacterial endocarditis. The blood urea nitrogen was found to be 74.9 mg. per 100 c.c., and the blood creatinine was 5.5 milligrams. A blood culture, taken to demonstrate the presence of *Streptococcus viridans*, yielded, instead, *Brucella*, uncontaminated by other organisms. An intradermal test with brucellergin gave a negative reaction, as was observed in the cases reported by Spink and Nelson.¹¹ The blood serum agglutinated *Brucella* in a dilution of 1:640.

There had been no previous history of rheumatic fever or heart disease. The patient had lived on a farm in Iowa, but knew of no evidence of brucellosis in his live stock. While the patient was in the hospital, his cattle were tested for evidence of Bang's disease, but none was found. The hogs were not examined, an oversight of frequent occurrence.

For descriptive purposes, the date of onset of the disease has been arbitrarily assumed to be Sept. 1, 1943. By this reckoning, the patient was admitted to the hospital on the one hundred and first day of the disease. The fluctuations in body temperature, the chemical studies of the blood, and the bacteriologic observations are recorded in the accompanying charts and tables.

Because of the azotemia and hematuria, the patient was encouraged to drink copious amounts of fluids. Within a few days, the daily urinary excretion varied from 1,000 to 3,000 cubic centimeters. By the one hundred and eighth day of the disease, the stupor was diminishing, and he appeared somewhat improved. The blood urea nitrogen and creatinine gradually diminished (Table I). Many examinations of the urine during the course of observation showed that the albumin gradually diminished in amount from 2 plus to a trace. Erythro-

TABLE I

*Blood Chemical Studies During Life**

DAY OF DISEASE	UREA NITROGEN (MG./100 C.C.)	CREATININE (MG./100 C.C.)	MISCELLANEOUS
102	74.9	5.5	Sulfonamide—trace van den Bergh: 1.2 indirect
107	63.7	4.5	
111	46.9	3.4	
113	39.2	4.1	
118	46.9	3.1	
125	32.9	2.4	
132	33.6	2.2	Serum albumin, 2.55 Gm.; globulin, 3.68 Gm.
140	34.3	2.4	
147	24.5	1.8	Urea clearance, 127 per cent
149	22.4	1.7	
157	23.1	1.9	
171	15.4	1.0	
188	14.0	1.0	

Bacteriologic Studies During Life†

DAY OF DISEASE	NATURE OF STUDY	RESULTS
105	Blood culture	<i>Br. suis</i>
107	Blood culture	<i>Br. suis</i>
110	Skin test with brucellergin	Negative
111	Agglutinins in serum	Positive for <i>Brucella</i> in dilution 1:640
114	Urine culture	<i>Brucella</i> and <i>Escherichia coli</i>
134	Blood culture	<i>Br. suis</i>
135	Agglutinins in serum	Positive for <i>Brucella</i> in dilution 1:320
178	Blood culture	<i>Br. suis</i>
181	Blood culture	<i>Br. suis</i>

*Determinations performed by the Department of Pathologic Chemistry.

†Bacteriologic diagnoses by the Department of Bacteriology.

cytes continued to be present in the sediment, but the number diminished with lessening of the azotemia. Some granular and hyaline casts were always present. The values of hemoglobin in the blood fluctuated between 8.5 and 12 Gm. per 100 cubic centimeters. Erythrocyte counts were recorded from 2,950,000 to 4,930,000 per cubic millimeter. The leucocytes varied between 2,800 and 6,050 per cubic millimeter. Serial electrocardiograms were normal except for left axis deviation and increasing negativity of T₃.

The faun-colored eruption disappeared within two days after admission. The edema of the ankles and the purpura subsided soon afterward, never to reappear. On the one hundred and eleventh day, the patient had a generalized convulsion lasting only a few minutes, but accompanied by extreme cyanosis. The blood pressure during the convulsion measured 185/130, but normal levels were afterward resumed. There were no residual neurological signs. It was thought possible that the patient had suffered cerebral embolism. On the one hundred and twenty-second day, a pain developed in the right knee and ankle, and migrated to the right hip. Roentgenograms of the pelvis showed evidence of spondylolisthesis and a separate neural arch; the body of the fifth lumbar vertebra had slipped slightly forward on the sacrum. This lesion was not attributed to brucellosis.

Slight, transient, painful swellings of the left ankle, left knee, right hand, and right knee appeared for periods of a day or so. Blood transfusions were given on the one hundred and twenty-first and one hundred and twenty-eighth days, but they were accompanied by such severe urticaria that repetition of the procedure was not attempted. Another troublesome symptom was an unproductive cough, unaccompanied by physical or roentgenologic evidence of disease in the chest. Some relief was obtained by steam inhalations.

On the one hundred and fifty-seventh day, the patient called attention to a painless mass in the left inguinal region. This proved to be an ovoid, pulsating tumor, 4.5 cm. in diameter, in the region of the left femoral artery, just inferior to the inguinal ligament. All pulsation had disappeared in the left popliteal, dorsalis pedis, and posterior tibial arteries. A clinical diagnosis of mycotic aneurysm of the left femoral artery was made. The size of the mass increased daily, with extension downward along the artery. The left foot and leg, however, remained warm and normal in color. A surgical consultant deemed ligation of the aneurysm inadvisable.

Therapy with sulfonamides was considered to be contraindicated by the renal lesions, and penicillin could not be obtained for the treatment of brucellosis. Convalescent serum was therefore prepared. Through the kindness of Dr. George H. Finch, of Des Moines, Iowa, a group of his patients agreed to serve as blood donors. All of them had recovered from severe infections with *Br. suis*, and bacteriemia had been present in every case, as shown by positive blood culture. Pooled serum was prepared by Dr. Carl F. Jordan, of the Iowa State Health Department, from the blood of ten of these patients. One hundred cubic centimeters of the pooled convalescent serum were given to our patient intravenously on the one hundred and seventy-eighth, one hundred and seventy-ninth, one hundred and eightieth, and one hundred and eighty-first days of the disease. There were no associated reactions. No definite change was noted in the condition of the patient; his temperature did not remain normal and the blood was not freed from organisms.

By the one hundred and eighty-fourth day, the condition of the patient was definitely worse. The aneurysm had attained a diameter of 10 centimeters. The walls appeared firmer. The patient was somnolent most of the time, and paresis of the facial muscles was noted on the right side. The left leg was weak and there was ankle clonus bilaterally. Saline and dextrose solutions were administered parenterally daily, together with thiamine chloride and nicotinamide. Twelve days later he had brightened considerably. The facial paresis had disappeared and his appetite had improved.

On the morning of the two hundred and sixth day, the patient experienced severe pain in the left groin which radiated down the leg. This increased over a period of several hours. Bright blood appeared in the urine. The scrotum became distended with fluid. The general condition, however, appeared good, and the blood pressure was maintained. During the next two days, the scrotum became discolored from extravasated blood. On the afternoon of the two hundred and eighth day, he complained of severe pain in the lower part of the abdomen, and died within an hour.

POST-MORTEM EXAMINATION

Autopsy was performed three and one-half hours after death.

General Inspection.—The body was that of a well-developed, well-nourished man, about 45 years old, showing a moderate degree of lividity posteriorly. Rigor mortis was present. The skin and mucous membranes were slightly icteric. A small amount of dependent edema

was present over the hands and ankles. There was a large diffuse swelling which involved the lower portion of the left lower quadrant of the abdomen and the left inguinal region. The skin in this area was not discolored, but the area of swelling was fluctuant. The scrotum was markedly edematous, and distended to five times the normal size. The skin on the scrotum had a bluish discoloration.

Peritoneal Cavity.—In the long axis of the left femoral artery there was a fusiform sac, 9 by 5 cm., lying both above and below the inguinal ligament. Externally, the sac was covered with adipose and areolar tissue which was heavily infiltrated with blood. Opening the sac revealed that it was lined with a thin, friable, gray membrane lying upon at least two other similar layers which were easily separated. No recognizable media or intima was visible.



Fig. 2.—Mycotic aneurysm of left femoral artery. Autopsy specimen in which the aneurysmal sac has been opened, showing walls composed of layers of fibrin. The pencil lies parallel to the intact femoral artery superior to the sac.

The femoral artery entered the superior pole of the sac, whereupon its structure was abruptly lost, to be resumed inferiorly (Fig. 2). On the superior surface of the sac was a hole, less than 1 cm. in diameter, through which blood had apparently extravasated into the retroperitoneal tissues along the left lateral portion of the abdominal wall to the left leaf of the diaphragm, spreading into the fan of the mesentery. In these regions the blood was present in clotted masses; the quantity was greatest near the left femoral artery and the left common iliac artery. Extravasation of blood had also occurred beneath the peritoneal covering of the sigmoid and descending colon. The scrotal sac contained a large amount of clotted blood which had infiltrated the fixed tissues. The peritoneal cavity contained about 100 c.c. of serosanguinous fluid, but no clots of blood were present. Microscopic examination of the wall of the aneurysm showed that it was composed of thick layers of fibrin. In some areas, portions of the arterial wall remained, but, for the most part, layers of fibrin were either superimposed on thin, partially hyalinized muscularis, or the fibrin lay directly on adjacent scar tissue. Masses of calcium were present in the muscular wall of the artery. Throughout the hyalinized layers of muscle and fibrin were nests of lymphocytes, monocytes, plasma cells, and large mononuclear cells. Small areas of fibroblastic proliferation were seen.

Pleural Cavity.—Both pleural cavities contained about 100 c.c. of clear, straw-colored fluid. The visceral and parietal layers were smooth and glistening, and no adhesions were present.

Mediastinum.—The organs showed normal relationships and no abnormalities were noted.

Pericardial Cavity.—The sac contained about 100 c.c. of straw-colored fluid. Everywhere the pericardium was smooth and intact.

Heart.—Weight, 350 grams. The size and contour were normal. The epicardium was smooth and intact; the epicardial fat was abundant. The cardiac chambers were normal in size and contained both fluid and clotted blood. The foramen ovale was closed. The endocardium of the left ventricle, beneath the aortic cusps, was slightly thickened and opaque. The measurements of the valves were: aortic, 6.5 cm.; mitral, 12 cm.; tricuspid, 13 cm.; and pulmonic, 6 centimeters. There were moderate, diffuse fibrosis and rolling of the free margins of the mitral leaflets, together with moderate scarring of the chordae tendineae. There was no suggestion of stenosis of the valve, however, and the degree of scarring was not more than is often seen with simple valvular sclerosis. These observations were not interpreted as evidence of rheumatic endocarditis. The anterior leaflet of the mitral valve contained a perforation measuring 7 mm. in diameter (Fig. 3). At the superior margin of the perforation was a friable, grayish-yellow vegetation, 1 cm. in diameter. Smaller, but similar, structures were implanted at the periphery of the perforation. Along the remainder of the line of closure there were small, pebbled masses, more firm and yellow than the large vegetations.



Fig. 3.—Perforation of the mitral valve. The photograph was taken forty-eight hours after the autopsy was performed. The friable vegetations had been removed previously for bacteriologic examination, and the valve leaflets had partially dried, so that they present the appearance of scarring in the photograph.

The vegetations were removed for bacteriologic study. The wall of the left ventricle measured 1.5 cm. in thickness, and that of the right ventricle, 0.5 centimeters. The myocardium was firm and beefy red. No abnormalities were noted on the cut surface. The coronary arteries were patent, but the walls contained occasional atheromatous plaques. With the microscope, moderate fragmentation of muscle bundles could be seen in some areas, but the cells were normal in size. Throughout the myocardium, especially in the interstitial tissue, there were small oval clusters of large, pale mononuclear cells, lymphocytes, plasma cells, and occasional polymorphonuclear leucocytes. These areas were more numerous near the endocardial surface. A few, small, round cells were scattered throughout the muscle fibers. There were no areas of necrosis and no Aschoff bodies. The blood vessels were normal, and the cell clusters bore no relationship to them. A section through a coronary artery showed the usual histologic changes of atherosclerosis.

Lungs.—The left lung weighed 380 grams, and the right, 400 grams. They were similar in appearance. The tissue was fluffy and contained air. A few emphysematous blebs were present along the superior margins. The bronchial mucosa was smooth and intact. There

was no congestion. The tracheobronchial nodes were normal. The cut surfaces of the lungs were dry and grayish pink. Histologic examination revealed that the pleura was normal. Many of the pulmonary acini were distended, and the walls thinned and ruptured. Patchy areas of fibrosis of the alveolar walls and interstitial tissue were numerous. These areas were infiltrated diffusely with lymphocytes, plasma cells, and large mononuclears. The bronchial epithelium in some areas was hyperplastic, and the peribronchial tissue contained zones of mild, chronic cellulitis. The blood vessels were normal.

Spleen.—Weight, 950 grams. The capsule was rather tense, but smooth and intact. The organ was softer than normal. On cut section, the Malpighian bodies appeared to be enlarged. The parenchyma was extremely pultaceous, and was reddish brown. Trabeculation was not visible. Near the lower pole there was a yellow area of necrosis, 1 by 2 cm., surrounded by a zone of hyperemia. A similar area was noted near the upper pole, but the latter was more firm and scarred. Microscopically, the splenic follicles were seen to be hyperplastic, and they contained small, hyalinized areas near their centers. There was diffuse hyperplasia of the reticuloendothelial elements. Throughout the pulp there were clusters of loosely arranged plasma cells, lymphocytes, and large mononuclears in no definite pattern. These masses were poorly circumscribed, but blended with the surrounding pulp. There were areas of congestion and the sinusoids were conspicuous. A large mass of scar tissue in one region contained old blood pigment and scattered round cells. In another section there was a large area of infarction, surrounded by a wide zone of extravasated blood. Fibroblastic proliferation was extensive at the periphery of the infarct.

Pancreas.—The gland was normal in size and consistency. Small, chalky plaques were visible on the cut surfaces. Microscopically, besides a moderate degree of autolysis, there were large areas of fat necrosis, surrounded by acute and chronic inflammatory reaction and some hemorrhage. There were patches of degeneration throughout. The fibrous tissue was increased in amount, and infiltrated with polymorphonuclear leucocytes and round cells.

Liver.—Weight, 1,240 grams. The contour was normal. The capsule was smooth and intact. The parenchyma was friable and brownish yellow. On cut section, the architecture was seen to be distorted by yellowish-gray, slightly elevated areas in the central zones of the lobules. Microscopic examination showed evidence of widespread parenchymal injury. There were atrophy, degeneration, and extensive necrosis of the liver cords. These changes were most marked in the central zones, but in many places the injury extended to the midzonal and portal areas. Fatty metamorphosis was present. Large amounts of lipochrome and hemosiderin-like pigments were seen. Islands of regenerating hepatic cells caused distortion of the architecture. There was no increase in fibrous tissue. Numerous round cells and a few large mononuclears were scattered throughout. In many places, these cells formed small nests in the areas of degeneration. Evidence of proliferation of the bile ducts was occasionally seen.

Gall Bladder and Ducts.—The gall bladder was normal in size and contained about 15 c.c. of clear, viscid bile. The mucosa was smooth, but the wall was moderately thickened and opaque. The ducts were patent. Histologically, the submucosa and muscularis of the gall bladder were seen to be edematous and infiltrated with small round cells and polymorphonuclear leucocytes. There was considerable fibroblastic proliferation.

Adrenal Glands.—Grossly, the glands appeared to be normal. Microscopically, there were slight autolysis of the cortex and some cortical atrophy. Occasional small nests of lymphocytes were noted.

Kidneys.—Each kidney weighed 210 grams. They were similar in appearance. The capsules stripped with ease, revealing smooth, pale, yellow surfaces over which were scattered many yellow nodules, varying from 1 to 2 mm. in diameter. Petechiae were abundant. The cortices measured 6 to 7 mm. in thickness. The architecture of the cortices was distorted in areas and obliterated by yellowish-gray streaks and numerous petechiae. The pyramids were well demarcated. From the area cribrosa, numerous yellow-gray streaks, similar to those in the cortices, ascended through the pyramids and caused considerable distortion of structure. The pelvic fat was abundant. The mucosa of the pelves was smooth and intact but marred by occasional areas of congestion.

Microscopically, there was evidence of diffuse nephritis, with focal areas of chronic granuloma. Many glomeruli were completely fibrosed and hyalinized; others showed crescentic scarring or were filled with erythrocytes. The glomerular lesions were extensive but patchy, and many glomeruli appeared normal. The tubules exhibited evidence of moderate, diffuse degeneration and atrophic changes. The epithelial cells were granular, and there was considerable sloughing of cytoplasm into the lumina. Many nuclei contained early pyknotic changes. In some areas, calcium salts were deposited in the tubular epithelium. The lumina

of many tubules were filled with erythrocytes and hyaline casts. Marked distortion of the architecture was caused by diffuse infiltration of the renal parenchyma with lymphocytes, plasma cells, and large mononuclears. In some areas, there was complete obliteration of normal structure. These inflammatory changes were particularly conspicuous in the cortex. In some sections there was a chronic granulomatous reaction, characterized by small areas of necrosis surrounded by epithelioid cells. No giant cells were seen. In some instances, the granulomatous reaction was intimately associated with small abscesses in which polymorphonuclear leucocytes as well as chronic inflammatory cells were present. Patchy zones of interstitial fibrosis were noted, particularly in association with the damaged glomeruli. The intima of a few medium-sized arteries was moderately thickened and hyalinized, but the walls of most vessels, including arterioles, were normal.

Pelvic Organs.—The bladder was contracted, but the wall was normal in thickness. Although the mucosa was smooth and intact, it was marred by granular plaques and several areas of extravasated blood. The prostate gland and seminal vesicles appeared normal. The testicles were normal, but they were embedded in a dense mass of blood extravasated in the scrotal cavity and in the areolar and adipose tissue of the scrotum.

Vascular System.—Throughout its course, the aorta exhibited a moderate degree of atherosclerosis. The walls contained discrete areas of calcification, but no ulceration was noted. The aneurysm of the left femoral artery has been described previously.

Lymphatic System.—The nodes in the pelvis, around the aorta, and near the celiac axis were moderately enlarged and red. Hemorrhages partly obliterated the architecture. Histologically, there was marked hyperplasia of the germinal centers. The endothelial elements were also hyperplastic. The sinusoids were dilated and filled with erythrocytes and large mononuclears. No areas of necrosis were noted.

Brain.—Permission for examination was not granted.

Anatomic Diagnoses.—Brucellosis; bacterial endocarditis (*Br. suis*), with perforation of mitral valve; dissecting mycotic aneurysm of the left femoral artery, with rupture and extension into retroperitoneal tissues; scrotal edema, with intrascrotal hemorrhage; recent and old infarcts of the spleen; diffuse nephritis, with focal areas of granuloma; extensive degeneration and necrosis of the liver; diffuse interstitial fibrosis of the pancreas, with fat necrosis and acute pancreatitis; chronic interstitial pneumonitis; pulmonary emphysema; sub-acute cholecystitis; and generalized icterus.

BACTERIOLOGIC STUDIES OF TISSUES POST MORTEM

Duplicate cultures were made on blood and tryptose agar plates from the heart valve vegetation, aneurysm wall, blood clot in the aneurysm, lymph nodes, spleen, and liver. One set of plates was incubated in an atmosphere of 10 per cent carbon dioxide, and the other set, under aerobic conditions at 37.5° C. These were examined at intervals of twenty-four, forty-eight, and seventy-two hours. Enormous numbers of *Brucella* colonies were found on the culture plates prepared from the endocardial vegetation, whereas only a few were noted in the other cultures. No colonies of streptococci or other significant organisms were noted on blood agar plates. Blood and tryptose agar plates, incubated under strict anaerobic conditions, failed to show any growth whatsoever.

After the preparation of the initial cultures, portions of the tissues were ground up in individual mortars, and saline suspensions made. Direct smears from the crushed vegetation revealed enormous numbers of pleomorphic, gram-negative bacilli, with the typical morphology of *Brucella*. Organisms were not found in the saline suspensions from other organs by stained smear.

Guinea pigs were inoculated with 0.25 c.c. of saline suspensions of the tissues, with the results noted in Table II. It is interesting that *Brucella* were isolated from the organs of the animals in two instances before the agglutinins appeared in the blood. In one case, *Brucella* agglutinins were absent on the seventh, twentieth, and fifty-eighth days after inoculation, whereas *Brucella* organisms were isolated from the organs of the animal on the twentieth and fifty-eighth days. These observations support the statements in the literature that *Brucella* may be isolated from the human blood prior to the demonstration of agglutinins. In some cases in which the diagnosis was verified by positive blood cultures, agglutinins were not detected throughout the course of the infection. Similarly, evidence of skin allergy may be lacking.

The organisms isolated from the tissues and the blood of this patient grew equally well on tryptose agar under 10 per cent carbon dioxide or under aerobic conditions. The morphology and the staining reactions were typically those of the *Brucella* group. Large amounts of hy-

TABLE II. RESULTS OF INOCULATION OF ANIMALS WITH SUSPENSIONS OF TISSUES

TISSUE FROM AUTOPSY OF PATIENT	GUINEA PIG	DAYS AFTER INOCULATION	GROSS LESIONS IN GUINEA PIG	TITER OF BRUCELLA AGGLUTININS IN GUINEA PIG SERUM	CULTURE FROM GUINEA PIG TISSUES
Spleen	1A	7	No lesions	Negative	Negative
Spleen	1B	20	No lesions	1:20	<i>Brucella</i> in all organs
Spleen	1C	35	Small abscesses in liver. Spleen enlarged and contain- ing abscesses. Abscess in groin	1:1,280	<i>Brucella</i> in all organs
Spleen	1D	58	Many abscesses in liver. Spleen enlarged and contain- ing many abscesses. Abscess in right groin	1:5,120	<i>Brucella</i> in all organs
Liver	2A	7	No lesions	Negative	Negative
Liver	2B	20	No lesions	Negative	<i>Brucella</i> in all organs
Liver	2C	35	Small abscesses in liver. Spleen enlarged with ab- scesses. Abscess in groin	1:10,240	<i>Brucella</i> in all organs
Liver	2D	58	Many abscesses in liver. Spleen enlarged. Abscess in groin	1:2,560	<i>Brucella</i> in all organs
Endocardial vege- tations	3A	7	Many small abscesses in liver	Negative	<i>Brucella</i> in all organs
Endocardial vege- tations	3B	20	Many abscesses in liver. Spleen enlarged with ab- scesses	1:640	<i>Brucella</i> in all organs
Endocardial vege- tations	3C	58	Many abscesses in liver. Spleen enlarged with ab- scesses	1:10,240	<i>Brucella</i> in all organs
Lymph node	4A	7	No lesions	Negative	Negative
Lymph node	4B	20	Few abscesses in liver	Negative	<i>Brucella</i> in all organs
Lymph node	4C	58	No lesions	Negative	<i>Brucella</i> in all organs
Wall of aneurysm	5A	7	No lesions	Negative	Negative
	5B	20	Many abscesses in liver. Spleen enlarged with ab- scesses	1:80	<i>Brucella</i> in all organs
Wall of aneurysm	5C	35	Many abscesses in liver. Spleen enlarged with few abscesses	1:640	<i>Brucella</i> in all organs
Wall of aneurysm	5D	58	Liver normal. Spleen enlarged with abscesses	1:1,280	<i>Brucella</i> in all organs

drogen sulfide were produced by the organisms in cultures incubated for five days. The organisms were agglutinated by polyvalent *Brucella* antiserum, and typed as *Br. suis* by the Huddleson bacteriostatic dye method.¹⁸

SUMMARY

The case of a man with *Br. suis* bacteriemia is reported. The infection lasted approximately two hundred days, during which endocarditis and nephritis developed. He recovered from uremia, only to succumb to rupture of a mycotic aneurysm of the left femoral artery. Sulfonamide therapy and the administration of convalescent serum failed to influence the infection. The pooled serum was prepared from the blood of donors who had recovered from *Br. suis* bacteriemia. Anatomic studies after death revealed, among other things, ulceration and vegetations on a previously normal mitral valve. The specific nature of the lesions was proved, during life, by the repeated isolation of *Br. suis* in pure culture from the blood stream, and, after death, by obtaining pure cultures of *Br. suis* from the vegetations from the endocardium, the walls of the mycotic aneurysm, and other tissues. The blood contained specific agglutinins, but the skin did not react to brucellergin intradermally.

So far as we are aware, this is the first reported case in which ulcerative endocarditis has been proved, beyond doubt, to be due to *Br. suis*. It is the second reported instance in which rupture of a mycotic aneurysm due to *Br. suis* has caused death.

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Clinical Reports

INTRACARDIAC FOREIGN BODY

REPORT OF A CASE WITH RECOVERY

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THE advent of the war has tremendously increased the incidence of traumatic wounds of the thorax due to various types of missiles. It is only natural, therefore, to expect that this increase should also be reflected in the more frequent occurrence of penetrating wounds of the heart. This case is being reported because of the unusual type of wound and the successful recovery of the patient.

CASE REPORT

J. L., a 21-year-old white radioman, was aboard a small boat that was patrolling the waters off the coast of New Guinea. On Nov. 11, 1943, at approximately 11 P.M., the lookout sighted two Japanese barges along the shore line, and the order to close in for attack was given. As they were approaching the barges, a Japanese battery, concealed on the beach, opened fire. The patient was standing erect with his arms slightly elevated and forward. During the melee, he was struck by several pieces of ricocheting shrapnel. He felt no severe pain at the time of the injury, but did experience a dull, constricting, nonradiating ache in the right side of the chest along with some dyspnea. He was given first aid treatment by the pharmacist's mate aboard, and was taken to an Army Field Hospital eight hours later.

At the time of admission, the patient was obviously in shock. There were shrapnel wounds of the lateral aspect of the right arm, some in the region of the right iliac crest, and one in his back on the right side near the angle of the scapula. Physical examination revealed diminished expansion, flatness to percussion, and absent breath sounds over the right lung. X-rays of the chest showed a hemopneumothorax on the right side, with considerable displacement of the heart and mediastinum to the left. A metallic foreign body superimposed upon the cardiac shadow was also noted.

The patient was treated vigorously for shock by repeated intravenous infusions of whole blood and plasma. He was also given oxygen and 1 Gm. of sulfadiazine three times a day. Several aspirations of the right pleural cavity resulted in the removal of large quantities of dark, blood-stained fluid and gradual re-expansion of the collapsed lung. The patient's condition steadily improved, and, on Jan. 15, 1944, he was transferred by plane to a Naval hospital facility for further study.

Upon admission at the latter institution physical examination disclosed a well-developed, pale, young adult in fairly good condition but somewhat tired from the plane trip. His temperature was 98.6° F.; pulse rate, 96; respirations, 18; and blood pressure 116/90. Systemic review revealed the following positive and cogent findings. There was a mild acne vulgaris eruption on the face. Several small, well-healed, nontender, irregular scars were noted along the lateral aspect of the upper portion of the right arm. Two similar, well-healed scars were observed just below the right iliac crest, and an erythematous, circular, tender scar approximately ½ inch in diameter was noted over the fourth rib posteriorly on the right side just below the angle of the scapula. The cardiac sounds were of good quality. There was a slight sinus arrhythmia. The second pulmonic sound was slightly more accentuated than the aortic second sound. There were no murmurs, thrills, or friction rub audible. Physical examination of the chest was essentially negative.

Laboratory study showed the following: erythrocytes, 4,200,000 per cubic millimeter; hemoglobin, 13 Gm.; leucocyte count, 6,600, with 65 per cent mature segmented polymor-

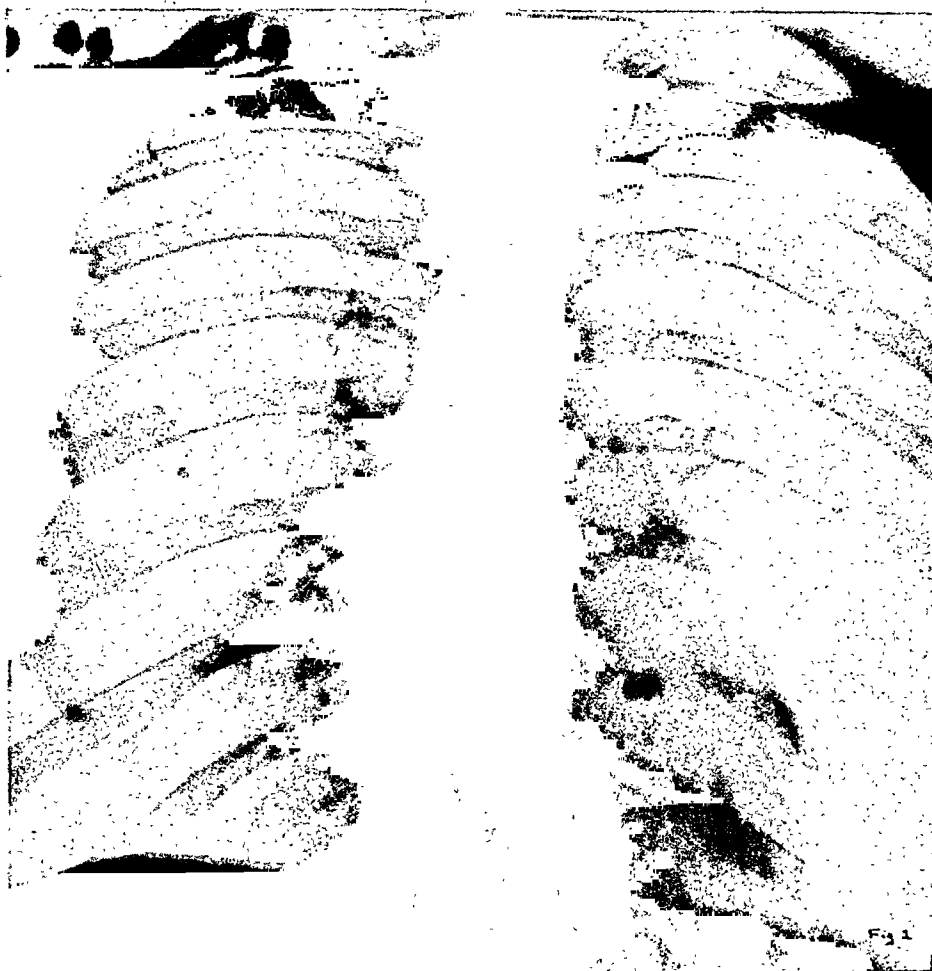


Fig. 1.—Posteroanterior view of chest showing foreign body superimposed upon the cardiovascular silhouette.



Fig. 2.—Right anterior oblique view showing the foreign body to be in the region of the conus arteriosus of the right ventricle.

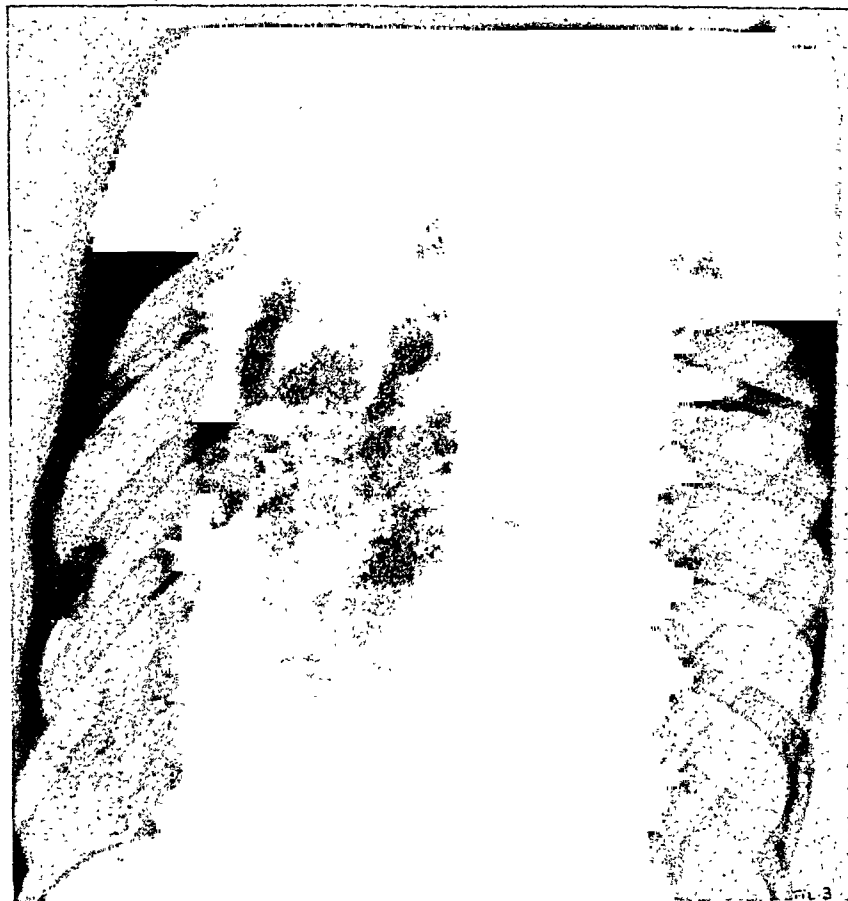


Fig. 3.—Left anterior oblique view.

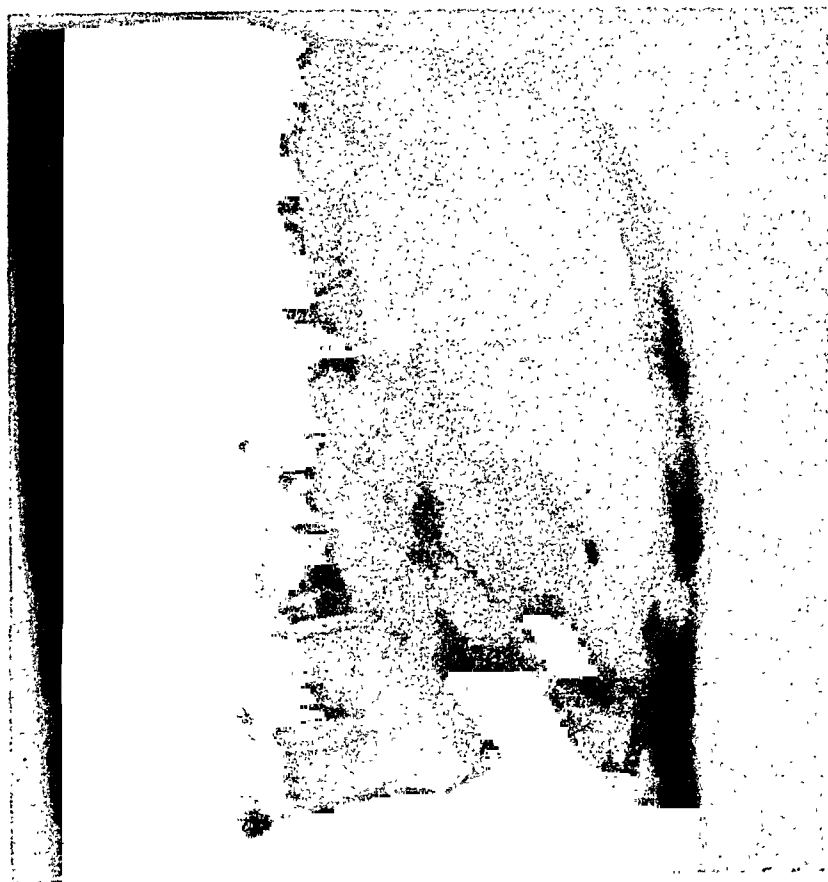


Fig. 4.—Left lateral view.

phonuclear leucocytes, 5 per cent nonsegmented neutrophils, 25 per cent lymphocytes, and 4 per cent monocytes. Urinalysis: specific gravity 1.020; albumin, negative; sugar, negative; and microscopic examination, 3 to 5 calcium oxalate crystals per high-power field.

Radiographic and fluoroscopic studies showed a rectangular metallic foreign body fragment, approximately 1 by 0.6 cm., embedded in the wall of the right ventricle in the region of the conus arteriosus. This fragment pulsed synchronously with the conus arteriosus and remained fixed when the patient was shifted into prone and lateral decubitus positions. There were also three small metallic foreign body fragments in the soft tissue on the right side below the level of the diaphragm. The fourth rib on the right side posteriorly near the axillary line was fractured. This represented the site of entry of the shrapnel fragment in the heart.

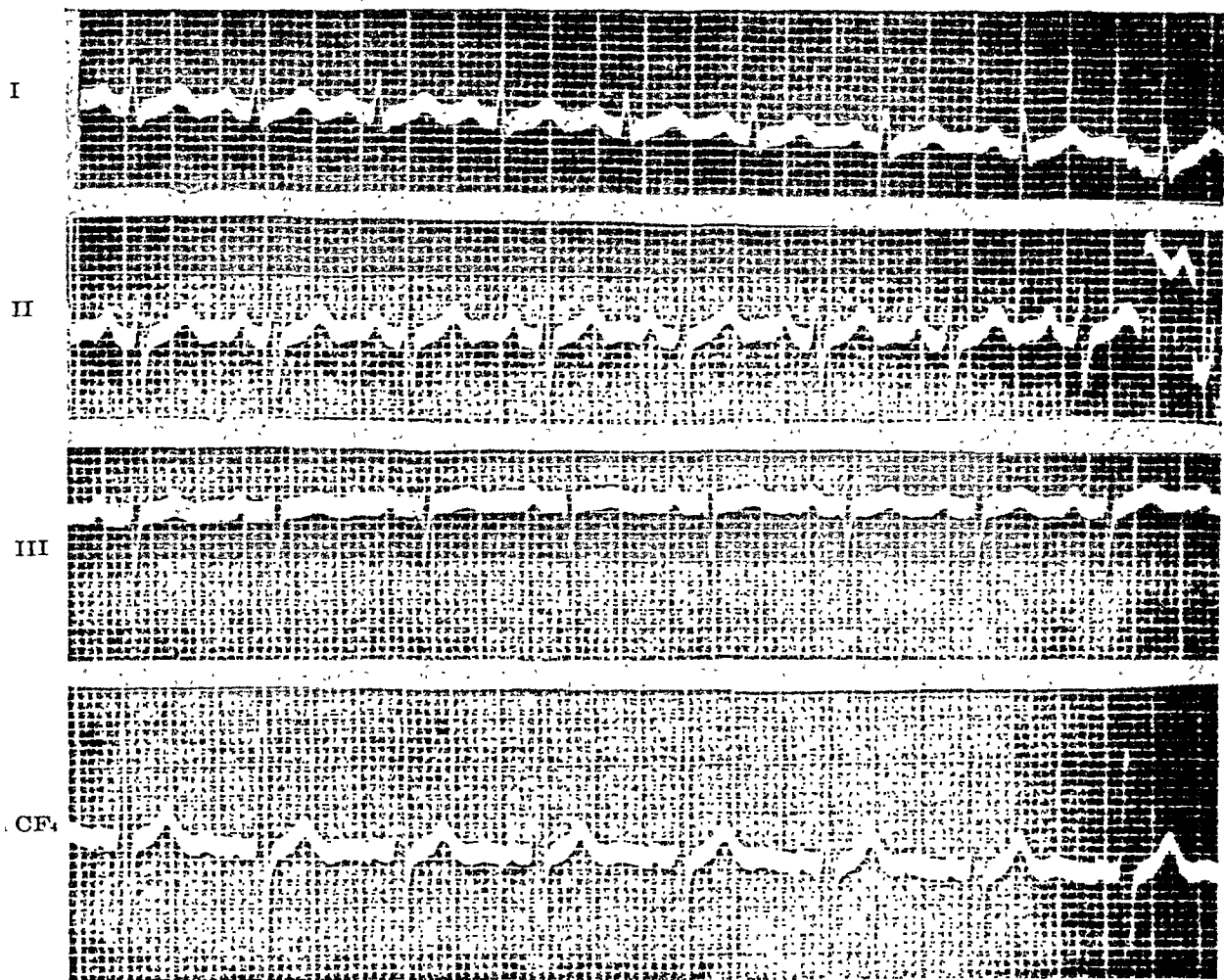


Fig. 5.—Electrocardiogram, taken Jan. 8, 1944, showing low voltage of QRS, left axis deviation, and slight sinus tachycardia (patient of sthenic habitus).

An electrocardiogram disclosed no abnormalities except a slight sinus tachycardia, low voltage of the QRS complex in Lead I, and left axis deviation; auricular rate, 100; ventricular rate, 100; P-R interval, 0.12 second; and QRS, 0.08 second. Leads CF_1 , CF_2 , and CF_4 were normal.

At the present time, the patient is entirely well clinically and has no cardiac symptoms or signs.

TRANSIENT HEART BLOCK IN CONGENITAL HEART DISEASE

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IN THE presence of congenital heart disease, heart block may be present as a functional part of the congenital defect or may occur as an acquired disturbance, superimposed upon the congenital deformity. The heart block may be complete or incomplete, transient or permanent. In the young, with recent acquisition of this defect in the absence of a history of infection such as syphilis (congenital or acquired), diphtheria, rheumatic fever, or chorea, and in the absence of overdigitalization, the causative factor producing the block is probably related somehow to a congenital defect. Vagal influence must be excluded.

Congenital heart block has been described many times and reviewed several times. Lampard¹ summarized thirty-one cases and reported one case. In many of the cases reviewed, attacks of syncope occurred. Later, Yater, Lyon, and McNabb² reviewed forty-four accepted cases of congenital heart block. The occurrence of syncopal attacks at an early age is accepted as good evidence of congenital heart block. These are, however, rare. Both of these reviews are concerned with cases of congenital heart block, *not* acquired *after* birth in the presence of congenital defects, but believed to have been present since birth.

Parkinson, Papp, and Evans³ collected and reported fifty-six cases of Stokes-Adams attacks with electrocardiograms taken during the attack and added eight more cases. They define Stokes-Adams disease as a name applicable to the condition of patients with heart block who suffer from recurrent attacks of loss of consciousness due to ventricular standstill, ventricular tachycardia, ventricular fibrillation, or a combination of these. In a true Stokes-Adams attack, the auricle continues to beat. In all, they found twenty-eight cases of Stokes-Adams disease with ventricular standstill and added five of their own. One patient was 16 years of age; the remaining varied in age from 29 to 78 years. The diagnosis of the underlying cardiac condition was not given in all cases. None were stated to have a congenital basis. They state that "no actual electrocardiogram of Stokes-Adams attack in congenital heart block has been found." Faessler⁴ collected eight cases of Stokes-Adams attack in congenital heart disease. Six cases had complete heart block between attacks. Six were diagnosed as patent interventricular septum, one as patent ductus arteriosus, and one as persistent foramen ovale. In Faessler's⁴ added case, there was no true heart block, but nodal rhythm was present during the period of unconsciousness. Between attacks the pulse rate was 120 to 140, with a normal electrocardiogram. The first attack occurred when the patient was 6 months old. During the attack, the pulse rate dropped to 22 and the electrocardiogram showed a nodal rhythm. In the other reported cases, auriculo ventricular block was present. Autopsy on Faessler's⁴ case showed transposed large vessels, double aortic arch, pulmonary stenosis, sub-aortic defect in the interventricular septum, and patent foramen ovale. The connecting auriculoventricular tissue was normal. However, there was intimal thickening on the main artery of the sinus node.

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Physiopathology of Stokes-Adams Attacks in Congenital Heart Disease.—

Septal defect is usually assumed to be present in the presence of congenital heart block. Fleming and Stevenson⁵ feel that the presence of heart block in congenital heart disease is an important sign, indicative of a defect in the posterior part of the interventricular septum. Leech⁶ described a case of congenital complete heart block associated with a patent ductus arteriosus where the possibility of a patent interventricular septum was not ruled out, but this was considered possible because of the presence of congenital complete heart block. This deduction is not fully justified as will be noted from the evidence to be presented. It is true that septal defect is the commonest deformity associated with heart block, yet, although a patent interventricular septum is the commonest congenital cardiac defect, congenital heart block is rather rare. This is probably due to the fact that the A-V bundle usually is behind the pars membranacea, while the defect is usually anterior. In instances where the defect is large, heart block may be absent. Lampard¹ correctly stated that patency of the septum is not the sole cause of the heart block. We know that as long as bundle fibers are present, though decreased in number, they may conduct an impulse. Theoretical physiologic considerations have been offered to explain the reasons for fluctuations in the conductivity of the bundle. These considerations relate to pressure, tension, or circulatory changes affecting the bundle and interfering with its conductivity.

a. Pressure and Tension Variations on the Bundle: Wilson and Grant⁷ found microscopically in a case of two-to-one heart block that dense fibrous tissue, instead of normally encircling the A-V bundle, had penetrated into the fibers of the bundle and had separated them into fine strands. They state "it is not difficult to imagine the fine strands being subjected to unusual pressure, especially in view of the circulatory failure shown by the patient during life." In the three cases studied microscopically by Yater, Lyon, and McNabb,² the A-V bundle showed imperfect development. Nisse,⁸ reporting a case of congenital heart block in a patient 1 year, 11 months old, noted that "slight variations in the degree of pressure on the bundle will probably account for the fact that in the case described the heart block is at times 2:1 and at other times complete." Lewis⁹ reported that alterations in tissue tension might abolish conduction in a bundle where it already was precarious. He described a case of heart block that developed suddenly in a woman in whom large venous sinuses separated the A-V bundle fibers. He attributed the attacks to intermittent swelling of the sinuses which interrupted conduction transiently by pressure. Smith¹⁰ described a 20-year-old man with congenital heart block. The electrocardiogram showed complete heart block except in forced expiration, when there was none. In this case, the heart was more horizontal in forced expiration and more vertical on inspiration. The decreased tension on the bundle during expiration supposedly released the blocking of impulse transmission. Calandre¹¹ presented a case with complete dissociation except in complete repose, when there was normal conduction. It is not unreasonable to suppose that an incomplete or variable dissociation could be due to slight variations of pressure on a tract, the tissues of which are abnormally surrounded or interrupted by fibrous tissue: the block varies with the tissue tension on the bundle strands. Brown¹² stated "it appears likely that for reasons of strain, heart block may be acquired in a congenital lesion."

b. Circulatory Variations Causing Block: Faessler's⁴ case, on microscopic study, revealed thickening of the intima of the main artery to the sinus node.

The Stokes-Adams attacks were attributed to marked decrease in blood circulation (during exertion) to the sinoauricular node due to the narrowed lumen, so that stimulus formation slowed down and the A-V node took over the function of pacemaker. Comeau¹³ summarized twelve cases and presented one additional case of attacks of complete A-V block with Stokes-Adams syndrome, alternating with normal rhythm. The patients varied in age from 43 to 78 years, and none had congenital heart disease. Comeau's patient later developed complete block, and the syncopal attacks disappeared. His conclusion regarding the mechanism of block production is that most cases are due to arteriosclerosis with some bundle damage. The fluctuating character of the conduction probably is determined by temporary variations in local circulation to the remaining intact fibers.

Whether symptoms develop during transient block, and what the severity of these symptoms will be, is dependent upon the duration of the circulatory arrest. However, other important factors are: the rapidity of onset of the block, the extent of decrease in rate, the blood pressure, the presence of anemia, the oxygen saturation of the blood, and the condition of the cerebral arteries. Symptoms are most apt to occur when complete heart block is interrupted by ventricular asystole of sudden onset, or when block occurs suddenly in the presence of normal rhythm.

Fleming and Stevenson⁵ stated that in the absence of gross cardiac abnormalities, the block per se causes little or no disability. They felt that most symptoms such as cyanosis, dyspnea, and syncopal attacks could be accounted for by the extent of the cardiac deformity, rather than on the degree of block. This opinion is not confirmed by a study of the literature where stress is laid on the point that a sudden increase in block, a slowing of the ventricular rate of sudden onset, or sudden appearance of block may cause Stokes-Adams attacks with syncope.

Leech¹⁴ stated that in a patient with congenital heart disease, and in the absence of causes such as pneumonia, epilepsy, meningitis, and severely toxic conditions, the occurrence of convulsive-like or epileptiform seizures may be interpreted as indicative of a lesion permitting a venous shunt. It is true that in infants, exertion and crying can cause convulsions and cyanosis in the presence of such a lesion. I should like to add transient heart block as another possible cause of similar symptoms in patients with congenital heart disease.

The case presented here is one of congenital heart disease, the lesion of which is clinically characteristic of patent ductus arteriosus, with no other evident associated lesions. Transient episodes of heart block occurred interrupting a normal rhythm. These episodes were associated with mild attacks of Stokes-Adams syndrome. A so-called typical electrocardiogram of congenital heart disease and the electrocardiogram of the block are presented, during the filming of which the patient fainted several times.

CASE REPORT

S. S., a man, aged 18 years, was known to have been born with "heart trouble." He had never been called a blue baby and never was known to have suffered cyanosis either at rest or on exertion. At school, he had always attended the cardiac classes and was restricted physically. He terminated his education after the seventh term in high school in order to go to work. There was no history of rheumatic fever, chorea, diphtheria, or congenital or acquired syphilis. He had always been capable of moderate exertion without dyspnea. He had no precordial pain, and no peripheral edema. The one symptom of which this patient was aware was a strong heartbeat, which often annoyed him as he

heard it pounding on his pillow at night. At the present time (November, 1942), he was employed as a shipping clerk in a dress factory.

On Nov. 22, 1942, a regular physical examination disclosed the following: A poorly nourished, underdeveloped white man, aged 18 years, 64 inches in height, and 96 pounds in weight. He was not acutely ill. There was no cyanosis or clubbing of the fingers or toes. There was no dyspnea. Eyes, ears, and nose were normal. Tonsils were neither enlarged nor infected. No cervical adenopathy was present. There was a marked increase in the pulsation of the neck vessels with a palpable systolic thrill.

Thorax: There were marked asymmetry of the chest, with precordial bulging, and narrowing of the intercostal spaces in the left axilla and posteriorly, while the spaces widened anteriorly. Systolic precordial interspace retraction was plainly visible. Marked kyphoscoliosis was present. The lungs percussed resonant except at the left base, where resonance was diminished. At this same area, bronchovesicular breath sounds were heard. The heart was markedly enlarged. The apex was felt in the sixth left intercostal space at the anterior axillary line. The entire precordium heaved with systole, while the strong apical thrust was felt separately. A fine systolic thrill was palpable over the second and third left intercostal spaces, adjacent to the sternum, which was transmitted into the cervical vessels. A short diastolic thrill was also felt in the second and third left intercostal spaces. On deep inspiration, these thrills disappeared. The area of cardiac dullness was outlined on percussion as follows:

	Right (cm.)	Left (cm.)
II	3.5	6.5
III	4.0	9.5
IV	3.5	14.0
V	3.5	15.0
VI	3.5	16.0

A loud systolic blowing murmur was heard over the entire chest, anteriorly and posteriorly, with greatest intensity over the second left intercostal space, then at the third left intercostal space and down the left sternal border. The pulmonic second sound was accentuated, and followed by a short diastolic murmur at the second left intercostal space. The systolic blood pressure was 150. At 40 mm. Hg a change in the character of the sound was heard, but thumping sounds could be distinguished down to the zero reading. A pistol shot could be heard in the groin, but Duroziez's sign was negative.

The abdomen showed nothing of note.

A circulation time with decholin gave an arm to tongue time of 13 seconds, which spoke against any veno-arterial shunt.

Fluoroscopy revealed marked cardiac enlargement with a very prominent, dilated pulmonary artery which showed exaggerated pulsations, filling synchronously with ventricular systole. The hilar "dance" was present. The transverse diameter of the heart measured 175 mm. at this time as determined by the rapid method.¹⁵ The blood Wassermann test was negative. The blood picture was normal. No polycythemia was present.

Four days later, on November 26, the patient was brought in. He had had several dizzy and fainting spells within the previous few hours, following undue and unusual exertion at a party where he had danced until 3 A.M. He had been feeling well until then but suddenly noted increased pounding of the heart, and periods where the heart seemed to "jump out of the chest and disappear into blackness." Periodic attacks of giddiness and faintness appeared. Transient periods of unconsciousness had been suffered lasting one minute or less. Because of the irregularity of the heartbeat noted, an electrocardiogram was taken at 6 A.M., three hours after the onset of the attacks.

The electrocardiogram (Figs. 1A and 1B) revealed the following: In Lead I, the auricles and ventricles follow each other at a regular rate of 100. The P-R interval is 0.16 seconds. At the end of the lead is noted a period of complete asystole, which merges into Lead II. Lead IIA starts with a complete heart block. The auricular rate is maintained at 100, while the ventricular rate drops to 39. The initial interval between ventricular systoles is 1.6 seconds.

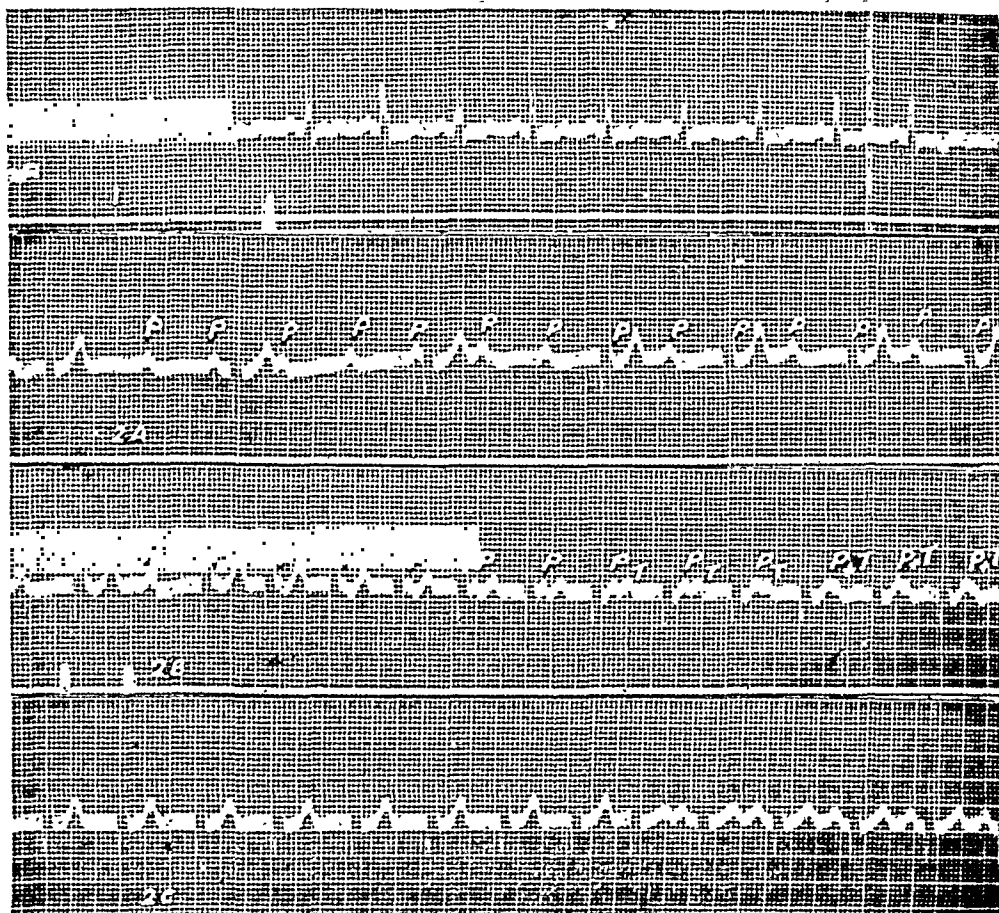


Fig. 1A.—Varying degrees of heart block in congenital heart disease. See explanation in text.

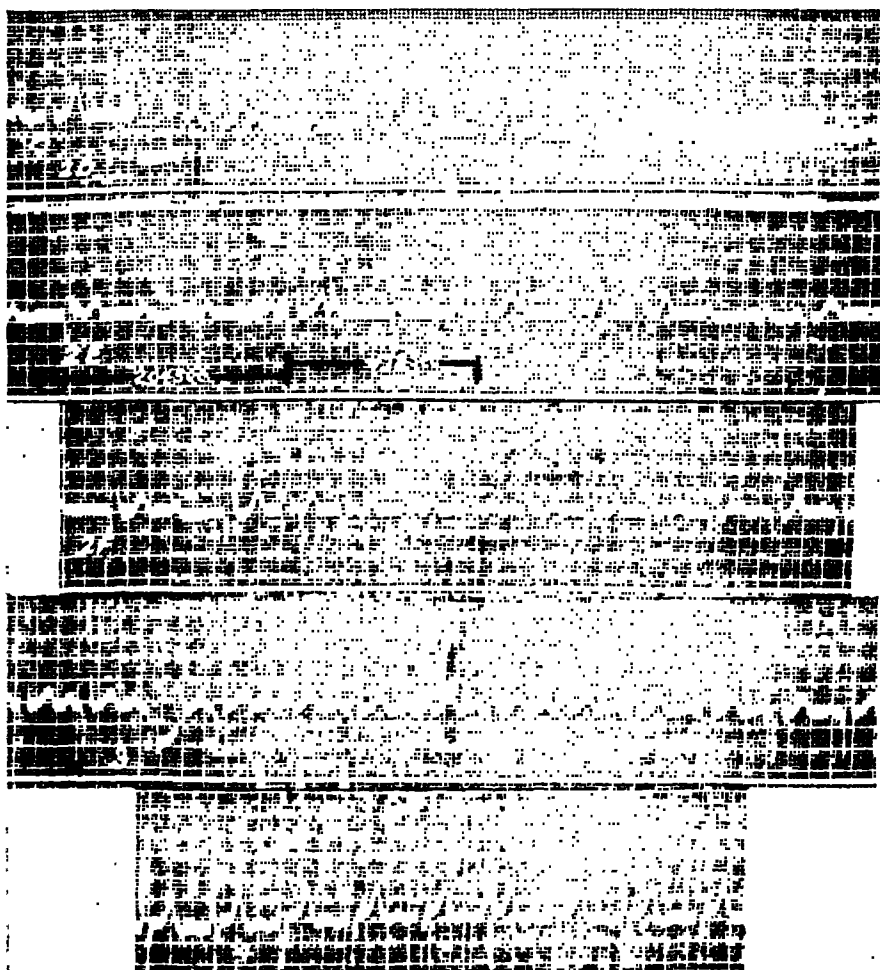


Fig. 1B.—This is a continuation of the electrocardiogram in Fig. 1A. See explanation in text.

In the second half of Lead II_A, the ventricle spontaneously increases its rate to 63, while the auricle continues at 100. In II_B, the auricle increases to 115, while the ventricles increase their rate to 100, each independent of the other. In II_C, the P and T waves merge, then separate. The first half of this lead appears as a prolonged P-R interval of 0.28 seconds with P and T merging, while the latter half shows no block, the P-R interval being 0.18 seconds with a sinus tachycardia of 100 being present. In II_D, we see a complete heart block followed by a two-to-one block, with the auricles at a rate of 110 and the ventricles at a rate of 55. The P is buried in the base of the descending limb of R. In II_E, complete heart block is evident with periods of ventricular asystole of 2.04

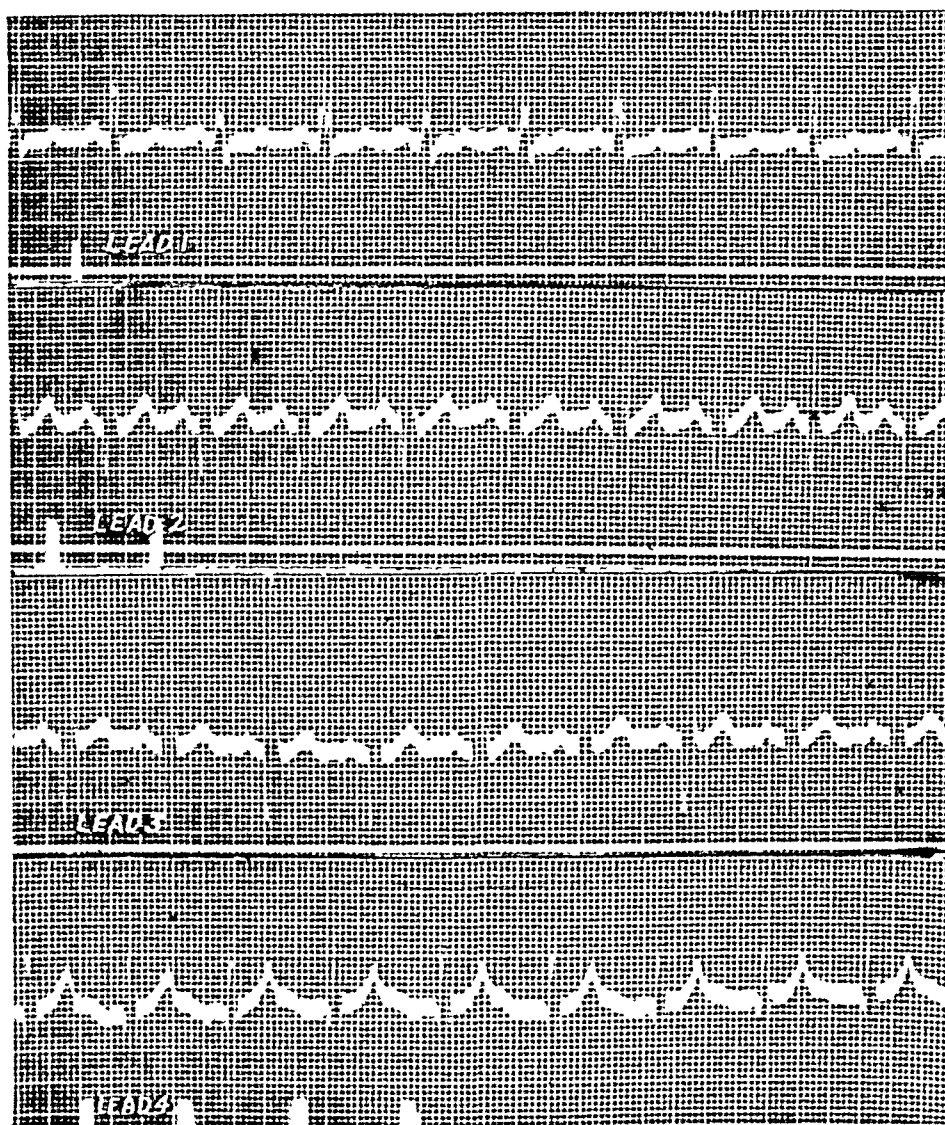


Fig. 2.—So-called typical electrocardiogram of congenital heart disease. Normal rhythm.

and 1.78 seconds. In II_F there is complete dissociation, with a rapid ventricular rate of 110. During the filming of Lead II the patient fainted for several seconds, and periods of light-headedness with sensations of faintness recurred. The attacks resembled those of petit mal. He constantly shook his head to throw off the sensation of faintness. No twitchings were observed. These were mild attacks of the Stokes-Adams syndrome. In Leads III and IV, there is a return to sinus tachycardia at a rate of 100 with a P-R interval of 0.16 second. It is to be noted in Lead II_F that complete dissociation exists with a rapid ventricular rate of 110. This is not uncommon in childhood where complete dissociation may exist with a rapid rate.^{6, 12}

A fluoroscopic examination was then made which revealed a transverse cardiac diameter of 185 mm. by the rapid method,¹⁵ indicating an enlargement of 10 mm., over the measurement taken four days previously. An injection of $\frac{1}{100}$ grain of atropine sulfate was given at this time. It had no effect on the recurrence of the fainting spells which continued for the next few hours. This indicated that the attacks were not due to a vagal influence. Ephedrine sulfate, $\frac{3}{8}$ grain, was given every three hours. Following the first dose two attacks occurred, but none appeared since then.

An electrocardiogram taken on November 30 (Fig. 2), showed a regular sinus tachycardia at a rate of 100. The P-R interval was 0.16 second. The widest QRS is 0.10 second, and is notched and slurred in Lead I. The diphasic character of QRS in Leads II and III are pathognomonic of congenital heart disease.¹⁶ Katz¹⁶ described such findings as being indicative of congenital defects in the septal conduction system, although in the case here presented,



Fig. 3.—Patent ductus arteriosus. Anteroposterior view.

there is no definite clinical evidence of a septal defect. The possibility of some imperfect development in the bundle fibers must be considered. Fluoroscopy at this time revealed a return in transverse diameter of the heart to 175 millimeters.

An x-ray (Fig. 3) taken on Dec. 2, 1942, was reported as follows: A markedly enlarged heart with diminished prominence of the aortic knob, marked prominence of the pulmonic curve, straightened left cardiac contour, and accentuation of the left ventricular curve. The measurements were: transverse diameter, 16.4 cm.; broad diameter, 13 cm.; long diameter, 18.3 cm.; transverse diameter of the chest, 26.2 cm.; and the cardio-thoracic ratio was 63. The angle of obliquity was 45 degrees. The pulmonary fields showed marked engorgement of the lesser circulation. In the right oblique view (Fig. 4) the arrow points to the pulmonary artery as seen on edge, with increase in

size evident. The dilated branches of the pulmonary artery are plainly visible. These findings agree with those of Donovan, Neuhauser, and Sosman¹⁷ in patent ductus arteriosus.

It becomes evident that heart block of varying degrees occurred following exertion. At the time of block, the heart diameter showed some widening transversely from 175 to 185 mm. (by the rapid method¹⁵) on fluoroscopy, evidently a dilatation. It is possible that during and following exertion, the increase in return flow of blood to the heart may have increased the pressure on the bundle of His which, with increase in the size of the ventricle, added tension to the bundle which varied in degree and caused a varying degree of heart block.



Fig. 4.—Patent ductus arteriosus. Right oblique view. Arrow points to pulmonary artery seen on end.

Whether the bundle is anatomically defective is not known. It is possible that there is a fibrous tissue disturbance interfering with conductivity. It is of interest to note Lampard's¹ statement that where heart block, murmurs, and enlargement are present "great caution should be enjoined and no games or violent exertion permitted" although each case must be judged individually. It is advisable to re-emphasize this enjoinder that undue exertion be interdicted in the presence of congenital heart disease, whether or not heart block is present.

SUMMARY

Varying degrees of heart block may occur in the presence of congenital heart disease, and cause mild Stokes-Adams attacks which conceivably could be more severe, with convulsions. The symptoms then are not due to the congenital heart disease but to the cerebral anoxia that follows the ventricular standstill. This condition may occur in congenital heart disease where no evidence of an interventricular septal defect is apparent.

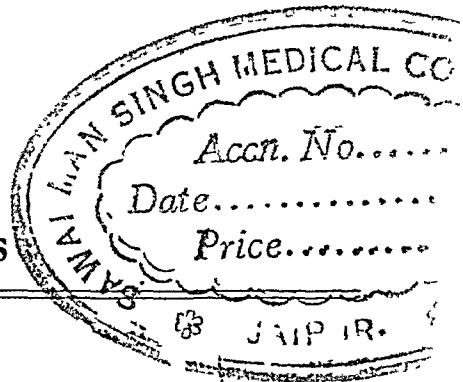
A case is presented with definite evidence of a patent ductus arteriosus, and no evidence of a patent interventricular septum, in which mild Stokes-Adams attacks occurred associated with the sudden onset of heart block, which varied in degree, was transient and followed by normal rhythm. This occurred following exertion, and was not of nervous origin. This is the first case to be reported of congenital heart disease with Stokes-Adams attacks in which an electrocardiogram taken during the attack is presented.

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Abstracts and Reviews

Selected Abstracts



Shipley, R. E., and Gregg, D. E.: The Cardiac Response to Stimulation of the Stellate Ganglia and Cardiac Nerves. *Am. J. Physiol.* 143: 396, 1945.

In confirmation of previous work, faradic stimulation of either the stellate ganglion or its cardiac branches in the anesthetized open-chest dog causes a considerable and sustained increase in coronary flow. Measurements of cardiac input and oxygen utilization have demonstrated that cardiac work and metabolism are also increased.

The cardiac nerves arising from the stellate ganglia are believed to be primarily involved in a mechanism by which the work output of the heart may be increased by nervous control. The promptness of the cardiac response and the somewhat prolonged aftereffect suggest the elaboration of a cardiac stimulating substance at the endings of the stimulated nerves.

The failure to obtain an increased coronary flow response without evidence of increased cardiac vigor, work, or metabolism, the lack of conclusive evidence that the cardiac nerves have a direct vasomotor influence, and the observation that cardiac metabolism is considerably increased, all lend support to the thesis that the increase in coronary flow may be largely, if not entirely, a secondary phenomenon. The increased vigor of cardiac contraction and the associated increase in cardiac metabolism resulting from nerve stimulation are regarded as the primary effects which indirectly give rise to coronary vasodilatation by (1) increasing locally the production and elaboration of metabolites, and/or (2) by creating a local relative anoxia caused by a disproportion between the increased rate of oxygen utilization and the existing coronary blood flow.

The role played by the cardiac nerves arising from the stellate ganglia is believed to be one associated with the adaptation of the work output of the heart to the blood flow and pressure requirements of the whole animal and not primarily one of coronary vasomotor adjustment to the requirements of the heart.

AUTHORS.

Moritz, A. R., and Weisiger, J. R.: Effects of Cold Air on the Air Passages and Lungs. *Arch. Int. Med.* 75: 240, 1945.

In this investigation, dogs were caused to breathe extremely cold air for periods ranging between twenty and one hundred thirty-three minutes. The rate at which air was warmed within the body was measured by means of appropriately placed thermocouples. The air was delivered to the larynx at temperatures which ranged between -50° and -28° C., and in no instance were temperature records lower than $+18^{\circ}$ C. observed at the bifurcation of the trachea.

The inhalation of cold air in circumstances such that intralaryngeal inspiratory nadirs as low as or lower than -30° C. were reached resulted in the development of a localized sublaryngeal tracheitis. In some animals the disturbance was limited to unusual activity on the part of the mucus secreting glands, and in others there was focal destruction of the superficial epithelium. In no instance was there evidence of primary injury to the lower portion of the trachea, the bronchi, or the lungs.

The aspiration of mucus or mucus and mucosal detritus from the upper portion of the trachea may result in the development of small and evanescent foci of pulmonary emphysema and atelectasis.

The explanation of the rapid warming of inhaled cold air and of the occurrence of relatively mild and localized injury following the inhalation of cold air lies in the fact that dry air has an extremely low heat capacity and that the number of calories required to produce a great rise in the temperature of dry air can be provided by the heat derived from the cooling of a small amount of tissue by a few degrees.

Although the intermittent exposure to cold air that occurs during normal respiration does not cause significant injury to the pharynx or larynx, a continuous exposure of these structures to cold may result in the development of a rapidly obstructive edema.

Experiments on dogs warrant the inferences (a) that it is unlikely that significant injury to the air passages of man would result from the breathing of air at any degree of coldness likely to be encountered in nonexperimental conditions so long as it was inhaled through the nose or between partially closed lips, and (b) that even though extremely cold air were inhaled rapidly through a widely opened mouth, it would be warmed to a point well above freezing by the time it reached the bronchi.

AUTHORS.

Dawson, P. M., and Hellebrandt, F. A.: The Influence of Aging in Man Upon His Capacity for Physical Work and Upon His Cardio-Vascular Responses to Exercise. *Am. J. Physiol.* 143: 420, 1945.

Observations on the capacity for physical work and the cardiovascular reactions during exercise were made upon a single subject. The latter rode a cycle-ergometer at 41, 53, 57, 68, and 71 years of age. During these rides the arterial blood pressures and pulse rate were usually determined, and the external work done was calculated for each ride. The results obtained support the following conclusions.

With age, working capacity fell off, becoming, at 71 years, about 50 per cent of what it had been at 41 years. When two rides are performed on the same day the score in the afternoon is greater than the score in the morning by about 3.5 per cent at both 57 and 68 years. The number of days necessary for complete recovery from a ride is greater at 68 and 71 than at 57 years of age. The circulatory reaction during maximal performance is much the same at all these ages. At 41 years the systolic pressure rose higher, but the ride which produced this pressure was only two-thirds as long as the rides performed later, and the tempo was much higher. The resting values of the systolic pressure whether lying or sitting on the cycle-ergometer did not change between 41 and 68 years of age. The maximum reduction of the resting pulse rate due to training is about the same at 41 and at 71 years. In training for a test on the cycle-ergometer the best preparation is to ride frequently upon this apparatus or to perform 3-mile runs. Road walking and mountain climbing do not yield as good results.

AUTHORS.

Sabathie, L. G., and Gaspary, F. V.: Unstable Auriculoventricular Heart Block, Permanent, Residual and Benign. *Rev. argent. de cardiol.* 11: 215, 1944.

An electrocardiographic study was made of four cases of unstable A-V blocks: a disturbance characterized by the mixture in variable proportions of high grades of partial A-V block with periods of complete block. The necessary conditions for the production of this type of A-V block are: (a) the lengthening of the postsystolic period of inexcitability due to the prolongation of the refractory period of the A-V node or bundle of His which determines at least a two-to-one partial A-V block; (b) a sinus rhythm of normal or slightly subnormal frequency and, in case of sinus tachycardia, a higher grade of A-V partial block; (c) a low ventricular rate as a result of the above mentioned conditions favoring the eclosion of an idioventricular rhythm of similar or slightly faster rate.

The cases reported are classified as unstable, permanent, residual, and benign A-V block. They are permanent, because they are unaltered during long periods of observation (two to fifteen years); residual, because no acute disease, intoxications, or organic heart disease could be found as a cause, the supposition being made that they are the result of a minimal myocardial alteration produced in the course of diverse minor pathologic processes; and benign, because they constitute the only manifestation of heart ailment, and have no evolutive tendency or grave repercussion on the circulatory capacity.

AUTHORS.

Goldberger, E.: The Basic Electrocardiographic Patterns in Bundle Branch Block. *J. Lab. & Clin. Med.* 30: 213, 1945.

When unipolar leads are used, the electrocardiographic patterns observed in cases of bundle branch block may be directly correlated with the actual spread of the impulse through the ventricles. On the basis of theoretical considerations and actual electrocardiographic observations, the following are the basic electrocardiographic patterns in cases of bundle branch block:

1. An M-shaped QRS complex in unipolar leads overlying or facing the affected ventricle and the affected side of the interventricular septum.

2. A W-shaped QRS complex from unipolar leads overlying or facing the contralateral normal ventricle and the normal side of the septum.

3. Prolongation of the QRS interval to 0.11 second or longer.

4. A negative T wave with the M-shaped QRS and a positive T with the W-shaped QRS, although exceptions to this are frequent.

5. The patterns observed with unipolar extremity and standard leads depend on the position of the heart. When the heart is vertical, the left leg lead will face the left ventricle and the left side of the septum. When the heart is oblique or horizontal, the left arm lead faces the left ventricle and the left side of the septum, and the left leg lead tends to face the right ventricle and right side of the septum.

Not every case in which the QRS interval exceeds 0.11 second is due to bundle branch block. In such cases the widening of the QRS interval is due to the fact that the impulse requires a longer time to penetrate a greatly hypertrophied ventricle than it normally needs.

AUTHOR.

Burrett, J. B., and White, P. D.: Large Interauricular Septal Defect With Particular Reference to Diagnosis and Longevity. *Am. J. M. Sc.* 209: 355, 1945.

Interauricular septal defects, which measure 1 cm. or more in diameter in individuals over 8 months of age, are of clinical significance and occur more frequently than do other congenital cardiovascular anomalies. Lesser defects are silent except in rare instances where they may permit the passage of small emboli from the right to the left auricle.

To avoid confusion as to the location of an interauricular septal defect, the suggestion is offered that it be described as being situated in the upper, middle, or lower portion of the interauricular septum.

A clinical analysis is presented of comparative studies in sixty-two autopsied interauricular septal defect cases collected before 1934 (by Roesler) with thirty-one autopsied interauricular septal defect cases collected since that date. There appears to be no definite sex preference. The size of the lesion beyond 1 cm. does not influence its symptomatic course or the longevity. Complicating mitral stenosis, except for occasionally associated auricular flutter and fibrillation, does not alter the picture after adulthood is reached. In a majority of cases, the patient is only mildly disabled from dyspnea and may withstand the ordinary physical and mental wear and tear accompanying the active life for years before succumbing to frank right heart failure. The average age of death lies between 36 and 37 years, and over 50 per cent of persons live beyond 40 years of age. Not uncommonly, individuals may pass the middle age mark without ill effects from this lesion, as demonstrated by Case 2. Complications, other than congestive heart failure, which is at times associated with terminal pneumonia, are conspicuous by their rarity. Only one case complicated by subacute bacterial endocarditis has been reported.

It is conceivable that secondary pulmonary arteriolar disease may develop in certain instances and be responsible for decreasing longevity. Pulmonary vascular lesions (sclerosis and thrombosis) were noted at autopsy in the authors' two cases. In the future, more careful microscopic examination of the pulmonary vascular bed should be accomplished.

The clinical recognition of interauricular septal defect cases has risen markedly in the past decade. A clinical diagnosis of nearly 50 per cent (fourteen of thirty-one cases) has been made since 1933, whereas previously only one in 62 cases was so diagnosed though considered in four other cases. Roentgen-ray investigation, electrocardiography, and a recognition of primary right heart involvement has been chiefly responsible for the recent percentage increase in diagnosis.

A further step in the recognition of these cases will be possible if roentgen-ray and electrocardiographic criteria are evaluated in lieu of certain associated symptoms and signs favoring an interauricular septal defect over pulmonary arteriolar disease as a cause for right heart embarrassment. In the latter instance, cyanosis is an early constant sign, longevity subsequent to the development of symptoms is short, and physical and roentgen-ray findings parallel the clinical course. In the former, mild dyspnea, usually without cyanosis, is an early and outstanding manifestation, and there is little or no disability for several years despite physical, roentgen-ray, and sometimes electrocardiographic findings indicative of rather marked right heart involvement. With these differentiating points in mind, it is believed that the diagnosis in the future will become possible in a much higher percentage of cases.

Left auricular pressure is apparently relieved by the passage of blood through an interauricular septal defect opening to the extent that there is little or no resultant left auricular enlargement despite coexistent mitral stenosis. The roentgen-ray picture remains that of pure right heart involvement. Therefore, mitral stenosis should offer no barrier to the diagnosis of a coexisting defect. On the other hand an interauricular septal defect, by effecting a reduction in the left auricular pressure, frequently results in disappearance of the mitral di-

astolic murmur as well as of left auricular enlargement in cases with mitral stenosis, and thus conceals the latter lesion. This fact is borne out by the discovery of coexisting mitral stenosis in nineteen of thirty-one autopsies in contrast to its clinical recognition in only nine of these cases.

AUTHORS.

Finland, M., Parker, F., Jr., Barnes, M. W., and Joliffe, L. S.: Acute Myocarditis in Influenza A Infections. *Am. J. M. Sc.* 209: 455, 1945.

Two cases with pathologic findings of acute nonbacterial myocarditis are reported. One of these patients died of cardiac failure and had a minimum of involvement of the lungs; the other died of an extensive acute bronchopneumonia from which no significant bacterial pathogen could be recovered. Influenza A virus was isolated from the lungs in both cases.

A review of the literature concerning the clinical and pathologic aspects of acute myocarditis complicating influenza and similar respiratory infections is presented. The relation of the influenza virus to the cardiac lesions in the present cases is discussed.

It is suggested that the myocardial lesions in these cases are the result of infection with influenza A virus.

AUTHORS.

Hamilton, T. R., and Hamilton, B. W.: Pathology and Bacteriology of Streptococcus Endocarditis in Relationship to Sulfonamide Chemotherapy. I. The Development of a Laboratory Technique for the Study of Chemotherapy in Vitro. *Am. J. Clin. Path.* 14: 495, 1944.

A simple, workable, laboratory technique for predicting the effect of drugs on organisms infecting the blood stream is presented. Sulfathiazole is effectively bacteriostatic within the therapeutic range, i.e., 406 mg. per cent, in fresh, whole, human blood, for streptococci of Lancefield's Groups A, B, C, and G.

Enterococci, represented by Group D streptococcus, and *Streptococcus fecalis*, were resistant to sulfathiazole in concentrations within the therapeutic range.

AUTHORS.

Hamilton, B. W., and Hamilton, T. R.: Pathology and Bacteriology of Streptococcus Endocarditis in Relationship to Sulfonamide Chemotherapy. II. The Effect of Temperature Elevation on the Action of Sulfathiazole Upon Endocarditis Strains of Streptococcus Viridans, Enterococci and Group A Streptococci. *Am. J. Clin. Path.* 14: 502, 1944.

These findings lead to the conclusions that the growth of the strains of viridans streptococci and enterococci tested by the method presented were enhanced at 40° C. Chemotherapy with sulfathiazole did not appear more effective at 40° C. than at 37° C. for these organisms, and in some instances it was less effective in whole, human blood as shown by a method that rather strikingly demonstrates the enhanced sulfathiazole effect on Lancefield's Group A, C-203 streptococcus at such elevated temperatures.

AUTHORS.

Call, J. D., Beggenstoss, A. H., and Merritt, W. A.: Endocarditis Due to Brucella: Report of Two Cases. *Am. J. Clin. Path.* 14: 508, 1944.

Two cases of endocarditis due to *Brucella* organisms have been presented with clinical and pathologic details. Among the peculiarities of this type of endocarditis are the tendency to involvement of the aortic valve, the tendency to ulceration and perforation, and the granulomatous nature of the visceral and neurological lesions noted in Case 2.

AUTHORS.

Gubner, R., Szucs, M., and Ungerleider, H. E.: Provocative Prolongation of the P-R Interval in Rheumatic Fever. *Am. J. M. Sc.* 209: 469, 1945.

Impairment of atrioventricular conduction of considerable degree was induced in twelve to sixteen subjects with rheumatic carditis by pressure on the carotid sinus. Similar pressure had produced no such impairment in sixteen control cases.

Preliminary administration of prostigmine augments the response in many cases.

The effect is more marked when the P-R interval is initially 0.18 to 0.20 second than when it is less than 0.18 second.

The changes in conduction are maximal during the acute stages of carditis and tend to disappear as rheumatic activity subsides.

It is suggested that this procedure enhances the diagnostic value of prolongation of the P-R interval in rheumatic fever.

AUTHORS.

Katz, L. N., Wise, W., and Jochim, K.: The Dynamic Alterations in Heart Failure in the Isolated Heart and Heart-Lung Preparation. *Am. J. Physiol.* 143: 507, 1945.

In the special heart preparations discussed in previous communications, cardiac failure was studied in twenty-two isolated heart and sixteen heart-lung experiments. The reasons for development of failure when the heart is removed from the body are unknown; failure eventually terminates the experiment. The manifestations of failure are (1) increase of one or both venous pressures without increase in cardiac output, and/or (2) decrease of cardiac output (pulmonary flow) and often also aortic pressure (the latter usually later if at all). Once initiated, cardiac failure pursues an apparently vicious accelerating course with the slopes becoming progressively steeper in their upward or downward trends, and especially when aortic pressure begins to fall the failure accelerates tremendously. All types of failure in the experiments are due to decreased power of the heart, but where the cardiac output and arterial pressures are level and the venous pressure rises on the left and/or right side, left and/or right "congestive" failure is present. In the presence of one or both types of failure the increased venous (i.e., auricular) pressures with increased diastolic volume, enable the work to be maintained. When the venous pressures do not rise, but work of the heart (cardiac output and/or arterial pressures) decreases, "forward" failure is present. Failure thus may be of the left or right "congestive" type, of the "forward" type, of combined left and right "congestive" type, or of "mixed" (congestive and forward) type. In general, the steepness of the slopes of the curves referred to is an expression of the degree of severity of the failure present.

Isolated Heart Preparation.—Aortic pressure fell in only half the cases of "forward" failure, and, in more than half of those in which it fell, the decline in aortic pressure was preceded by a decline in cardiac output; in three experiments both began to fall at the same time. Delayed or absent fall in aortic pressure is due in some to decline in coronary flow with the consequent increase in coronary resistance being sufficient to maintain the total resistance of the two parallel circuits through which the left heart output is distributed. The usual cause, however, for the maintenance of aortic pressure is the existence of a critical level of aortic pressure and cardiac output about which changes of the latter do not appreciably affect the former. This is due to the peculiar relationship of these two in the existent distensible circuit discussed in the text and more fully in a previous report. This fall in arterial pressure is a sign of advanced, rather than early failure. In congestive failure per se, aortic pressure remained constant. Pulmonary pressure relationships are similar to those of aortic pressure, except that coronary resistance increase cannot help maintain pulmonary pressure. In left congestive failure, the equivalent of a gap in the circuit in the isolated heart preparations was responsible for the lack of rise of pulmonary arterial pressure.

With left or right "congestive" failure, left or right venous pressure rose in an accelerating fashion. The development of "forward" failure lessens the rate of rise or even produces a fall, distorting the otherwise exponential type of curve. The venous pressures are increased by the congestion consequent upon decreased power of the heart but are decreased by the lessened load of the heart when the work declines in "forward" failure. Regurgitation due to dilatation of the atrioventricular valve rings in advanced failure may contribute to the rise of venous pressures. Decreased cardiac tonus in failure may lessen this rise.

Coronary flow changes in "congestive" failure, that is, changes in the partition of the cardiac output, occur as in nonfailing hearts. In "forward" failure coronary flow usually decreases when cardiac output falls. Delay or absence of decrease was due, in our experiments, to (1) continuance of spontaneous coronary dilatation present before "forward" failure; (2) increase in peripheral resistance due to adjustment to keep aortic pressure from falling; and (3) increase in peripheral resistance due to decreased distention of the resistance tubing as the aortic-vena cava flow decreases. Thus, no changes in coronary flow occur which are peculiar to heart failure per se.

Calculated work of the heart was found to be similar to cardiac output except when marked "forward" failure was associated with a drop in arterial pressures. However, severe "congestive" failure significantly lessens the true work of the heart since with pressure already high in the blood as it returns to the heart, less work is necessary to raise the pressure to the same degree of arterial pressure. This has been neglected in ordinary calculations of work, which have hitherto ignored initial pressures of the entering blood.

Closed-Circuit Heart-Lung Preparation.—Apart from the fact that in these experiments artificial maintenances of constant cardiac work (when possible) delayed or prevented "forward" failure, changes were essentially similar to those occurring in the isolated heart, except with regard to pulmonary arterial pressure and left venous pressure. Due to the ab-

sence of artificial separation of the pulmonary artery and "pulmonary veins," pulmonary arterial pressure rose in left congestive failure. Moreover, pulmonary edema, when present, caused an accentuated rise in pulmonary arterial pressure and lessened the left venous pressure rise. Both factors lessened the tendency of pulmonary arterial pressure to fall in some cases when "forward" failure developed. In the isolated heart, a similar difference was seen between those experiments in which cardiac output was maintained constant and in those in which it was not.

Effect of Increase in Load.—On several occasions, increasing the cardiac output or artificial resistance initiated or accentuated failure as manifested by the changes in venous pressure. Similarly, in severe failure increasing the blood volume sometimes increased the venous pressures but not the cardiac output, and withdrawing blood sometimes reversed this effect.

AUTHORS.

Ricca, R. A., Fink, K., and Warren, S. L.: The Effect of Sulfadiazine, Antitoxins, Globulins, and Dog Plasma on Dogs in Traumatic Shock Under Sodium Pentobarbital Anesthesia. J. Clin. Investigation 24: 146, 1945.

The hazard entailed in giving anesthesia during traumatic shock is not increased by therapeutically effective concentrations of sulfadiazine in the blood stream.

The authors have been unable to detect any beneficial effect of sulfadiazine on traumatic shock, although it does reduce the incidence and amount of gas development from *Clostridium welchii* in the tissues of the traumatized site.

The results on the intravenous administration of 18 Gm. of protein as horse globulin are suggestive that the procedure is beneficial to the clinical course of traumatic shock in dogs under nembutal anesthesia in an environmental temperature of 28° C.

The experiments emphasize the important role that environmental temperature may play in experimental traumatic shock, in determining the survival rate of the animal. They suggest that a study of the effect of therapeutic agents such as gas gangrene antitoxins and plasma should be made at high environmental temperatures (28° C. and above), where the usual survival rate of the traumatized animals is low.

AUTHORS.

Katzin, L. I., Ricca, A. R., and Warren, S. L.: Effect of Environmental Temperature and Anesthesia on the Survival of Tourniquet Shock in Rabbits. J. Clin. Investigation 24: 149, 1945.

The temperature of the environment greatly affects survival rates of rabbits on whom tourniquets have been applied for five hours. At 16° C. and below, survival rates are high; at 24° C. and above, survival rates are low. This is in agreement with the findings in crush injury by means of the press in dogs.

Nembutal anesthesia may possibly affect the survival rate since 26 per cent (five out of nineteen rabbits) survived when nembutal was used, and 41 per cent (fifteen out of thirty-six rabbits) survived when no anesthesia was employed in controlled experiments. The room temperature was in the lethal range of 24° C. to 28° C.

AUTHORS.

Katzin, L. I., and Warren, S. L.: Thiamine-Deficient Diet in Tourniquet Shock in Rats. J. Clin. Investigation 24: 152, 1945.

In rats, a thiamine-deficient diet for various periods (eleven to thirty-nine days) had no appreciable influence on the survival rate from shock produced by a tourniquet.

AUTHORS.

Scholz, D. E., Schultz, J. H., Pleune, F. G., Fink, K., Steadman, L. T., and Warren, S. L.: Study of the Body Temperature and Water Content in Shock Produced by the Continuous Intravenous Injection of Adrenalin, With and Without Anesthesia. J. Clin. Investigation 24: 151, 1945.

Nembutal anesthesia results in a generalized parallel fall in the subcutaneous, intramuscular, and rectal temperatures of the dog.

Injection of adrenalin under the conditions described has no effect on the rectal temperature. The peripheral muscle temperature drop is accentuated.

On the basis of survival time, nembutal anesthesia appears to have a deleterious effect in adrenalin shock.

Applications of heat to the four extremities, in an attempt to raise the peripheral temperatures to normal, did not result in a beneficial effect in adrenalin shock.

In general, the hematocrit was elevated as a result of the injection of adrenalin.

The initial rise in arterial blood pressure when the adrenalin injection is begun is followed by a fall which continues fairly steadily until the animal succumbs.

The most significant finding in the change in percentage of water in the tissues as a result of adrenalin shock was an increase in water content of the heart. Pericardial effusion usually occurs, and edema of the heart was also demonstrated histologically. The quantity of water involved is of no significance to the total water balance.

The findings indicate that, in this type of shock, there is no specific mobilization of water in the tissues which accounts for the rather frequent finding of a rise in hematocrit (hemoconcentration).

Serum potassium and sodium showed no consistent changes. A rather consistent increase (average of 17 per cent) in serum magnesium was found in those dogs given nembutal anesthesia and was attributed to the latter.

AUTHORS.

Linton, R. R.: Arterial Embolism. A Simplified Technique for the Removal of a Saddle Embolus at the Bifurcation of the Aorta With a Report of a Successful Case. Surg., Gynec. & Obst. 80: 509, 1945.

The success of an embolectomy depends on: (1) early operation, (2) direct and adequate exposure of the site of embolism, (3) occlusion of the artery distal to the embolus before the artery is disturbed at, or proximal to, the site of embolism, (4) avoidance of damage to the intima, (5) complete control of the arterial inflow both proximal and distal to the arteriotomy so that (6) a meticulous intima-to-intima closure may be accomplished.

The removal of a saddle embolus at the bifurcation of the aorta is a feasible operation if these principles are followed.

The technique of the operation has been simplified by the use of the tourniquet type of clamp for control of the arteries during the embolectomy.

A saddle embolus at the bifurcation of the aorta may be removed readily through an arteriotomy of the right common iliac artery, with two clamps on this blood vessel and one on the left common iliac artery, without the necessity of freeing up the aorta.

Embolectomy is more readily accomplished by direct exposure of the site of embolism. For this reason a transperitoneal or extraperitoneal approach through a right paramedian incision is recommended for the exposure of the bifurcation of the aorta and the common iliac arteries.

AUTHOR.

Naide, M., and Sayen, A.: The Primary Influence of Basal Vascular Tone on the Development of Postocclusive Collateral Circulation and in Selecting Patients for Sympathectomy. Am. J. M. Sc. 209: 478, 1945.

An objective method is described by which one can predict whether a collateral circulation is likely to develop following a major peripheral arterial occlusion and whether a sympathetic ganglionectomy is indicated. By determining the patient's basal vascular tone, which can be obtained from any unoccluded extremity, it is possible to predict far more accurately the course of the disease and to decide the amount and type of treatment required.

Patients who have a low grade of vascular tone will develop a collateral circulation almost invariably and, as a rule, do not require much treatment. The majority of patients who have a high grade of vascular tone do not develop a collateral circulation; and, since their symptoms are much more severe, require intensive treatment. Only patients with a high grade of vascular tone require sympathetic ganglionectomy.

The previous method for selecting patients for sympathectomy on the basis of their capacity to vasodilate in response to paravertebral or local nerve block is erroneous. The patients who are in most urgent need for sympathectomy are those with high basal vascular tone who do not respond to temporary nerve block. Patients with low vascular tone are not improved by sympathetic ganglionectomy.

AUTHORS.

Bain, C. W.: Pericarditis and Complete Heart Block During Thiouracil Therapy. Brit. Heart J. 7: 49, 1945.

A case of pericarditis with complete heart block is described in a patient receiving methyl thiouracil for thyrotoxicosis. The tonsils were infected, but there was no previous history of rheumatism.

AUTHOR.

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ALTERATION IN P-R INTERVAL ASSOCIATED WITH CHANGE IN POSTURE

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INTRODUCTION

IN THE past five to six years, the recording of many thousands of electrocardiograms in healthy normal men for the purpose of aircrew or other military medical examinations has brought to light many interesting examples of "so-called" electrocardiographic abnormalities in healthy normal men without any apparent evidence of heart disease.

During a study of the routine electrocardiograms of Royal Canadian Air Force aircrew in 1940-1941 four cases were discovered which showed significant alteration in the P-R interval with change in posture. In one of these the reduction in the P-R interval was very marked, from 0.40 second to 0.20 second on changing from the recumbent to the upright position.

It has been shown by several workers that alterations in the direction and amplitude of the wave complexes are sometimes associated with changes in posture and respiration.^{1, 3, 5, 6, 8, 9} Changes have also been reported in the P-R interval and other time relationships in association with heart disease and with various physiologic factors.^{4, 11}

A case of persistent functional heart block apparently due to vagal influence has been reported by Poel.⁷ In this case a change in posture from lying to standing position changed the P-R duration from 0.36 second (standing) to 0.30 second (sitting). Poel also reviews three other cases of incomplete heart block due to vagal effect. The effect of posture, however, was not determined. Case 4 of the present report is of particular interest in that incomplete heart block is present in the recumbent position and abolished in the sitting or standing position. It differs from Poel's case in that the P-R duration comes within the accepted limit of P-R duration and therefore is not a case of persistent A-V block. The mechanism, however, is most likely due to a vagal effect as discussed in Poel's report.

MATERIAL AND METHODS

Routine electrocardiograms were taken on R.C.A.F. aircrew trainees in 1940 and early 1941. The men were between the ages of 18 and 32 years, the majority between the ages of 18 and 26 years. All had passed the standard R.C.A.F. medical examination at a Recruit-

ing Center. A complete clinical recheck was made, one or two months later, by a Medical Selection Board, and at that time the electrocardiograms were recorded.

The routine electrocardiograms were taken with a portable Cambridge (English) electrocardiograph which recorded the three standard leads on a single film. The deflection of the galvanometer string was standardized before each lead was recorded. All the records were taken in the recumbent position.

As mentioned in previous reports,^{2, 8} a considerable number of abnormal electrocardiographic findings were noted, including 2.2 per cent of records with a P-R interval greater than 0.20 second.

One group of twenty men whose original electrocardiograms had shown a prolonged P-R interval were recalled for further investigation, including the effect of changes in posture and respiration on the electrocardiogram. The first record of this special study was also taken in the recumbent position. It was compared with the previous one and served as a check on the recording technique. It was also used as a basis for comparison of further records, taken immediately afterward in different postures and phases of respiration.



Fig. 1.—A, Case 3. Recumbent; prolonged P-R interval; negative P waves. B, Case 3. Sitting, normal P-R interval; positive P waves.

OBSERVATIONS

A. Decrease in Prolonged P-R Interval With Postural Change.—Of the twenty men whose electrocardiograms showed a prolonged P-R interval, four had a record in which this interval could be altered by change in posture. In Case 1, a reduction occurred in the P-R interval from 0.28 second in the record taken in the recumbent position to 0.20 second in the one taken in the sitting position. The change in position was accompanied by only a slight increase in the heart rate.

In Case 2, the P-R interval decreased from 0.24 second in the record taken in the recumbent position to 0.20 second in the sitting position, without significant change in heart rate.

In Case 3 the routine record revealed negative P waves in all three leads, a P-R interval of 0.24 second, a left axis deviation, a splintered S_3 wave, and a negative T_3 wave (Fig. 1, A). One week later additional records were taken in the recumbent position, in the sitting position, in the sitting position following deep inspiration, and in the recumbent position following exercise. The record taken in the recumbent position was the same as the routine record described previously, with a heart rate of 79 per minute. In the sitting position the P

waves in all three leads became positive, the P-R interval was reduced to 0.20 second, and the heart rate was unchanged (Fig. 1, *B*). T_3 was still negative, but the splintering of S_3 had disappeared. This produced a more marked degree of left axis deviation. Deep inspiration in this position did not change the P wave or P-R interval, but reduced the degree of left axis deviation. After one minute of strenuous exercise a record taken in the recumbent position showed negative P waves in all three leads again. The heart rate was increased to 100 per minute and the P-R interval was 0.20 second. Left axis deviation and splintered S_3 were still present, but T_3 was now positive. It appears from the alteration in direction of the P waves that there may have been a shift in the location of the origin of the impulse within the auricle when the airman moved from the horizontal to the vertical position. On physical examination no cardiac abnormality could be detected.

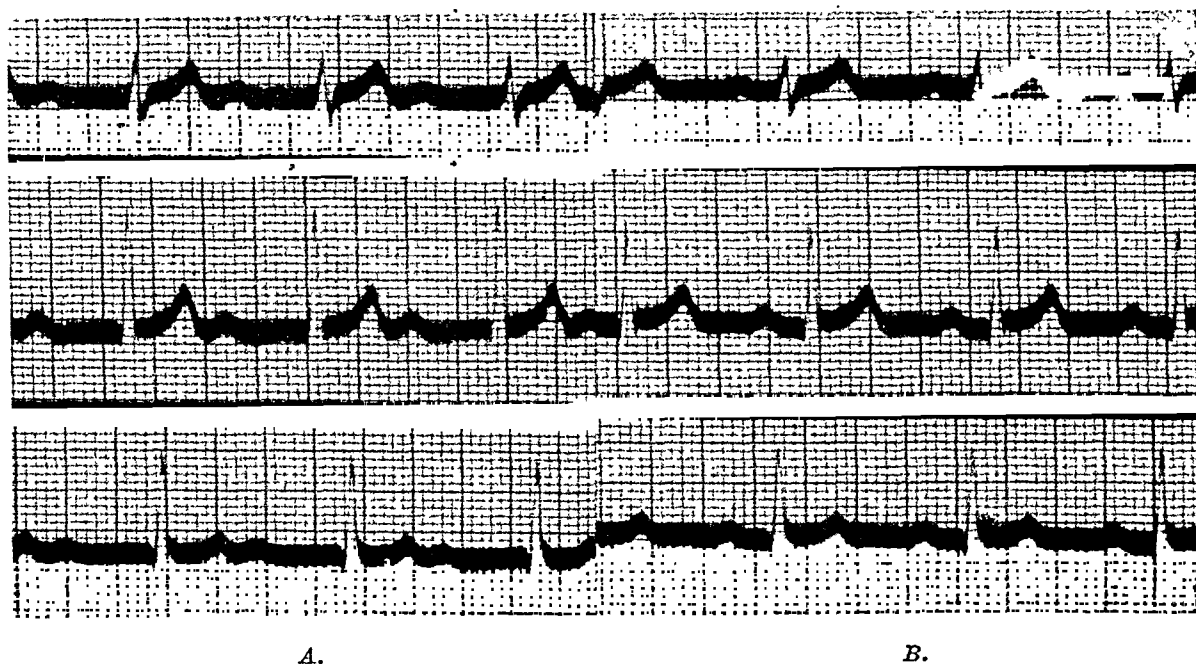


Fig. 2.—*A*, Case 4, 1940. Recumbent; prolonged P-R interval. *B*, Case 4, 1940. Sitting; normal P-R interval.

Case 4 was a healthy athletic airman, aged 25 years, whose clinical examination revealed no abnormality. Blood pressure was 130/88. Heart size and sounds were normal. The original electrocardiogram, taken in the recumbent position in July, 1940, showed a P-R interval of 0.40 second (Fig. 2, *A*). In the sitting position the P-R interval became 0.20 second (Fig. 2, *B*) with little or no change in the heart rate from that shown in the preceding record.

Additional records were taken in the sitting and recumbent positions, following exercise, and following the subcutaneous administration of $\frac{1}{100}$ grain of atropine sulfate. In the recumbent position the P-R interval was again 0.40 second, and deep inspiration only reduced it to 0.36 second. Thirty minutes after the subcutaneous injection of $\frac{1}{100}$ grain of atropine sulfate the interval in the recumbent position was still 0.36 second.

Nine days later another series of electrocardiographic records was obtained. The man was placed in the recumbent position, and records were taken at various angles by elevating the head of the bed. In the recumbent position the P-R duration was again 0.40 second. At 40 degrees from the horizontal it was still 0.40 second, but at 50 degrees it had changed to 0.20 second. The elevation of the bed was not continuous. There was a pause for several minutes while each

TABLE I. CHANGES IN P-R INTERVAL
(Case 4, 1940)

POSITION	INTERVAL	HEART RATE
Recumbent	0.40	84
25 degrees from horizontal	0.40	82
40 degrees from horizontal	0.40	84
50 degrees from horizontal	0.20	84
60 degrees from horizontal	0.18	84
70 degrees from horizontal	0.20	86
80 degrees from horizontal	0.20	84
Standing	0.20	88
Recumbent	0.40	78
On right side	0.42	66
On left side	0.42	66
Prone	0.44	70
Carotid sinus pressure	0.42	70
Immediately after exercise	0.24	110
Two minutes after exercise	0.36	94
Three minutes after exercise	0.36	96

record was made. Table I shows the P-R interval and cardiac rate in the various positions.

In the right or left lateral or prone positions there was a slight increase in the P-R interval beyond 0.40 second accompanied by a slight decrease in the heart rate. The last three records in Table I were taken immediately after the man had exercised until he was almost exhausted. The heart rate was 110, and the P-R duration was reduced to 0.24 second. A few minutes later the heart rate had decreased to 94, and the P-R interval had increased to approximately 0.34 or 0.36 second. It could not be measured accurately since the P wave was partially superimposed on the T wave.

The remarkable alteration in the P-R interval with change from the recumbent to the upright position was observed over a period of one month. Since there was no evidence of cardiac abnormality other than that found in the electrocardiogram he was permitted to continue his flying training.

An additional electrocardiogram obtained in January, 1942, revealed the same findings with a P-R interval of 0.36 to 0.38 second in the recumbent position. He had been on operational flying overseas as a fighter pilot for several months and showed no clinical evidence of cardiac abnormality. Further examinations were made in April, July, and August, 1943, when the officer was hospitalized for duodenal ulcer. Clinical cardiac examinations at this time were negative, but no electrocardiogram was taken.

On March 3, 1944, after the officer's return to Canada, an electrocardiographic record showed a P-R of 0.34 second, and on March 9, 0.32 second. The latter record was said to have been taken in the sitting position.

On March 28, 1944, he was referred to a consultant cardiologist who reported that in the recumbent position the P-R interval was 0.34 second, and in the sitting position it was 0.32 second. Eyeball pressure did not affect the P-R interval significantly, but after exercise a record in the recumbent position showed it to be 0.19 second with a rate of 108.

On April 17, electrocardiograms were taken by the same cardiologist with the subject in the sitting and recumbent positions before and after the subcutaneous injection of $\frac{1}{50}$ grain of atropine sulfate. In these records the P-R interval was reported to be normal, 0.16 second, in the sitting position and 0.32 in the recumbent. Atropine did not change the P-R interval in either position.

The medical documents therefore report two electrocardiograms with prolonged P-R interval which were said to have been taken in the sitting position,

TABLE II. CHANGES IN P-R INTERVAL—CASE 4—1944

POSITION	P-R INTERVAL (SEC.)	HEART RATE (PER MIN.)	FIGURE
1. Recumbent, normal respiration	0.38	62	Fig. 3, <i>A</i>
2. Recumbent, deep inspiration	0.36 to 0.40	60	
3. Recumbent, deep expiration	0.38 to 0.40	64	
4. Sitting, normal respiration	0.20	65	Fig. 3, <i>B</i>
5. Sitting, deep inspiration	0.22 to 0.38	74	} Fig. 4
6. Sitting, deep expiration	0.24 to 0.38	72	
7. Standing, normal respiration	0.20	82	
8. Lying, right side	0.36	60	
9. Lying, left side	0.36	60	
10. Recumbent, immediately after lying down	0.22	66	Fig. 5
11. Recumbent, 1 minute after lying down	0.38	62	
12. Standing, immediately after exercise (T and P partly superimposed)	0.20 to 0.24	146	
13. Standing, 4 minutes after exercise (T and P partly superimposed)	0.20 to 0.24	130	
14. Eight minutes after exercise, immediately after lying down	0.22 to 0.24	90	
15. Recumbent, immediately after exercise	0.18	90	Fig. 6
16. Recumbent, 3 minutes after exercise	0.20	84	
17. <i>Tilt Record 1</i>			
1. From horizontal to 80° in 20 seconds	0.36 to 0.24	70 to 80	
2. At 80° for 10 seconds	0.24 to 0.20	86	
3. From 80° to horizontal in 20 seconds	0.20 to 0.24	76	
4. Horizontal	0.36 immediately	66	
18. <i>Tilt Record 2</i>			
1. From horizontal to 80° in 11 seconds	0.36 to 0.34	70	
2. At 80° for 8 seconds	0.30 to 0.20 in 4 seconds		
19. <i>Tilt Record 3</i>			
1. From horizontal to 80° in 10 seconds	0.36 to 0.22	66 to 80	
2. At 80° for 10 seconds	0.22	82	
3. From 80° to horizontal in 16 seconds	0.22	80	
4. At horizontal 7 seconds	Still 0.22	70	
20. <i>Tilt Record 4</i>			
1. From horizontal to 80° in 18 seconds	0.36 to 0.24 (at 70°)	70 to 80	Fig. 7, <i>A</i>
2. At 80° for 10 seconds	0.20	84	
3. From 80° to horizontal in 20 seconds	0.24 to 0.36 (at 10°)	80	Fig. 7, <i>B</i>
4. Horizontal for 10 seconds	0.36	72	

but other records taken a few weeks later did not confirm this. A possible explanation for this apparent contradiction was shown in the following series of records obtained in August, 1944. These were taken on a Cambridge electrocardiograph-stethograph (research model). Table II shows the P-R interval as measured in Lead II and the cardiac rate of the records obtained at this time in various postures and phases of respiration.

In electrocardiograms taken after the subject has been in the recumbent position for a few minutes the P-R interval was 0.36 to 0.40 second (Fig. 3, *A*). Records taken in the sitting or standing position had a P-R interval of 0.20 seconds (Fig. 3, *B*). These were similar to records taken four years before (Fig. 2, *A* and *B*). It was noted, however, that when he was tilted from 80 degrees to the horizontal the P-R interval sometimes did not increase for several seconds. For example, in Record 17 the P-R interval increased immediately from 0.24 to 0.36 second as the horizontal level was reached, but in Record 19 the P-R interval was still 0.22 second when the record was stopped seven seconds after reaching the horizontal level. Record 10, taken immediately after the officer lay down, also showed a normal P-R interval (Fig. 5). Apparently the change in P-R interval does not always occur immediately after change in posture. In the same way, on tilting quickly from horizontal to 80 degrees

(Record 18), the P-R remained prolonged for a few seconds before changing to 0.20 second. This may explain the occasional finding of a prolonged P-R interval in records taken in the sitting position, as reported in his medical documents, if these records were taken immediately after sitting up.

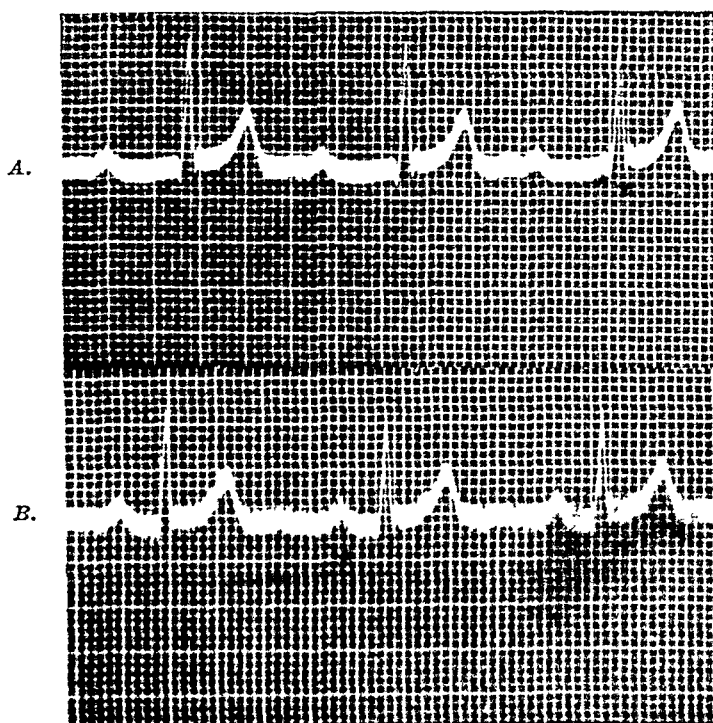


Fig. 3.—A, Case 4, 1944, Lead II. Recumbent; P-R, 0.38 second. B, Case 4, 1944, Lead II Sitting; P-R, 0.20 to 0.21 second.

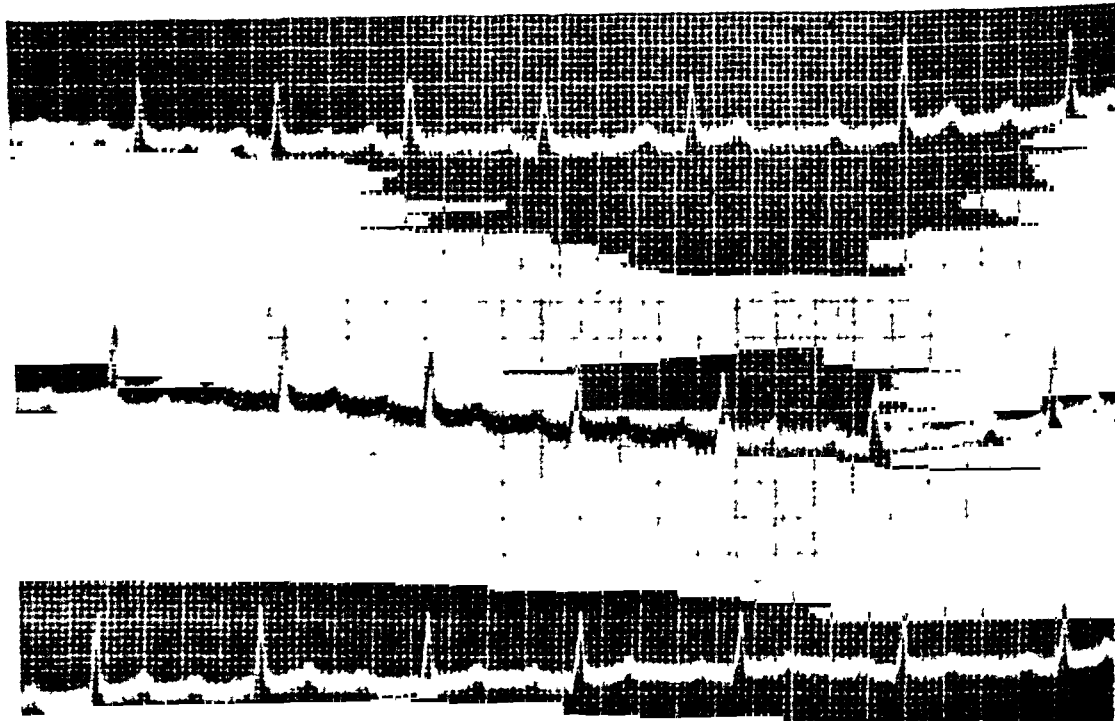


Fig. 4.—Case 4, 1944, Lead II, continuous record. Sitting. Top: P-R increased from 0.22 to 0.38 second with deep inspiration. Middle: P-R decreased to 0.24 second on expiration and increased to 0.38 second on forced expiration. Bottom: P-R returned to 0.22 second with normal respiration.

Deep inspiration and deep expiration both prolonged the P-R interval in records taken in the sitting position (Fig. 4), but no significant change was produced by deep breathing in records taken in the recumbent position where the P-R interval was already 0.36 to 0.38 second.

The exercise carried out before Record 12 consisted of stepping to a chair twenty-five times per minute for three minutes. The electrocardiogram taken while standing showed a P-R interval of 0.20 to 0.24 second immediately after the exercise and four minutes later with the P wave partly superimposed on the preceding T wave. Eight minutes later and immediately after lying down it was still 0.20 second with a rate of 90. It was thought that this short P-R interval in the recumbent position might have been due to the fact that the record was taken soon after the patient assumed the recumbent position and was not due to exercise. However, records were taken on the following day with the subject exercising the legs for two minutes, as in riding a bicycle, while retaining the recumbent position. The pulse rate was increased to 90, and the P-R was reduced to 0.20 second by the exercise alone (Fig. 6). It was apparent,

Fig. 5.

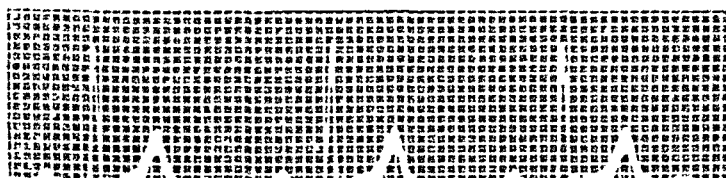


Fig. 6.

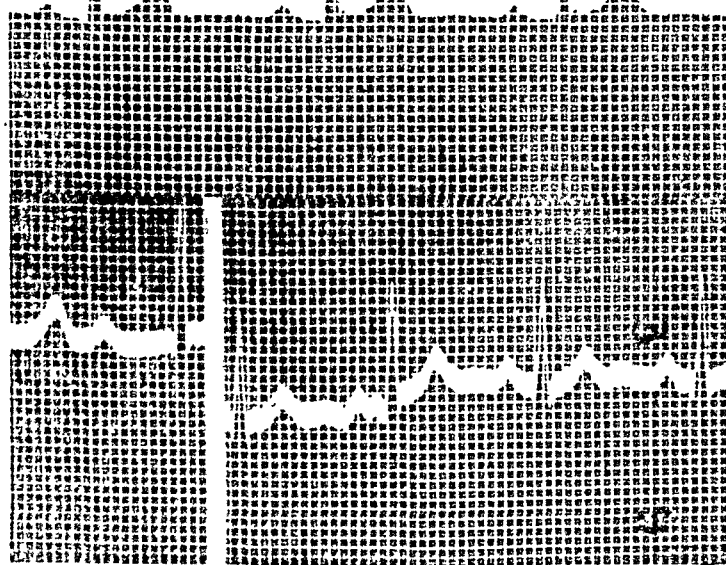


Fig. 5.—Case 4, 1944. Recumbent, immediately after lying down. P-R interval 0.22 second.

Fig. 6.—Case 4, 1944. Recumbent, immediately before and after exercise. P-R interval decreased from 0.36 to 0.18 second.

therefore, that exercise was capable of reducing the P-R to the normal range, even without an excessive increase in rate, while the man remained in the recumbent position. Exercise also resulted in the P-R remaining short if the recumbent position was assumed before the rate had returned to normal. Unfortunately the records were not continued until the change in P-R interval occurred.

During the movement of the tilt table the electrocardiogram was recorded continuously. It was noted that the P-R change usually occurred just as, or shortly after, the body reached the upright or horizontal position, although Record 19 was discontinued before the change occurred. In records taken four years before, the change in P-R interval was noted between 40 and 50 degrees. However, the latter had been taken after a pause at each 10-degree angle, and

TABLE III

POSITION	LEAD I	LEAD II	LEAD III
1. Recumbent, normal respiration	0.13	0.16	0.16
2. Recumbent, deep inspiration	0.14	0.15	0.15
3. Recumbent, deep expiration	0.15	0.16	0.16
4. Sitting, normal respiration	0.14	0.15	0.15
5. Sitting, deep inspiration	0.13	0.15	0.15
6. Sitting, deep expiration	0.14	0.15	0.16

there was a time interval of several seconds sufficient to allow the adaptation of the P-R interval to occur.

B. *Changes in Normal P-R With Postural Change.*—A study was also made of the changes produced by posture and respiration in P-R intervals within the range of 0.12 to 0.18 second. The electrocardiographic records of thirty men were studied, and the results were compared with those of the prolonged P-R group. Electrocardiograms were taken in the recumbent position and the sitting position during normal respiration, following deep inspiration, and following deep expiration. The heart rate and P-R intervals were measured in each record. Table III shows the average duration of the P-R interval with each position.

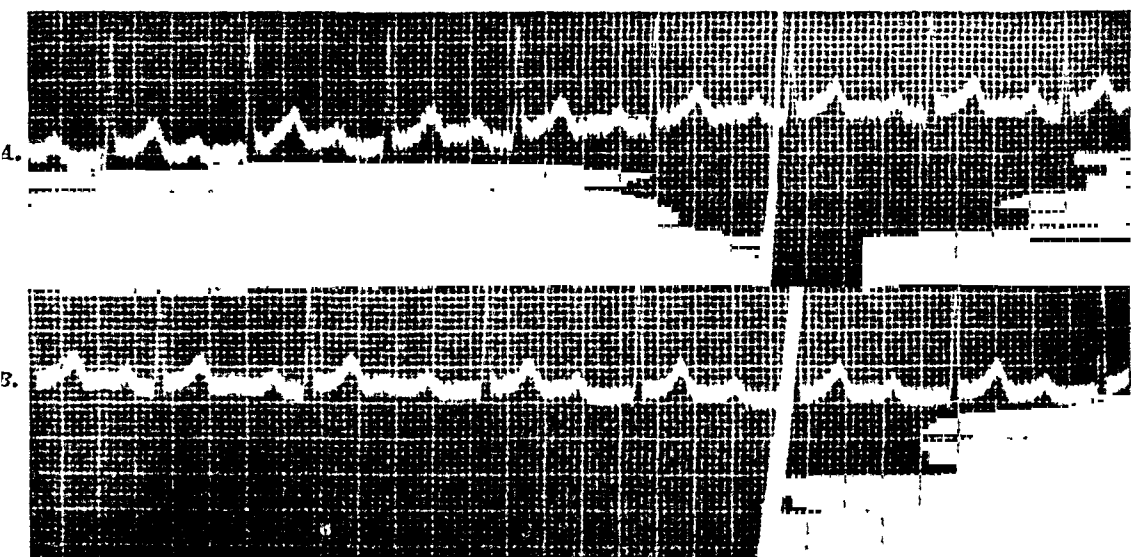


Fig. 7.—A, Case 4, 1944. Tilt to 80 degrees (white line). P-R interval decreased from 0.36 to 0.20 second. B, Case 4, 1944. Tilt back to horizontal (white line). P-R interval increased from 0.20 to 0.32 second at angle of 10 degrees.

Slight variations in the P-R interval and also the P-wave amplitude occurred in many of the records. This change was usually about 0.01 and 0.02 second. In the records of six men a decrease in P-R interval of 0.02 second accompanied an increase in heart rate produced by a change from the recumbent to the sitting position.

In one other man a P-R interval of 0.18 second and a heart rate of 88 were noted in the record taken in the recumbent position. In the sitting position the rate remained at 88, but the P-R became 0.16 second. On deep inspiration with the man remaining in the sitting position, the interval decreased to 0.12 second. This change is in the reverse direction from that noted in Case 4. The heart rate remained practically the same, 84 per minute, and there was a marked decrease in the amplitude of the P waves with P_3 changing to a negative wave.

DISCUSSION

A number of individuals have shown interesting changes in the P-R interval associated with changes in the posture and respiration and with changes in

heart rate produced by exercise. This study has not produced evidence as to the exact nature of these changes, but it is suggested that two possible explanations might be considered—an aberrant conduction pathway or fluctuation in vagal tone (autonomic imbalance). Lewis⁴ and others have shown that increase in the vagal tone in the human being produces many effects on the cardiac mechanism, some of which are seen in the electrocardiogram. These vagal effects are more apparent in convalescent patients, and as a result fainting often occurs.

In this group of four men the first electrocardiograms, taken in the recumbent position, would be considered abnormal insofar as the P-R interval is concerned, while their records taken in the upright position would be considered within the normal limits, or borderline. It is considered possible that the physiologic fluctuations in autonomic balance may be more prominent in these men than in the average individual. The vagal effects might be so marked that the P-R duration would be increased beyond the accepted normal limits. Vagal effects usually produce minor changes such as sinus arrhythmia and bradycardia,¹⁰ but they might be responsible for even greater effects in these individuals. It is not understood why the change in posture should be responsible for the production of such effects.

In electrocardiograms with a P-R interval between 0.12 and 0.18 second, only slight alteration occurred in the P-R duration as a result of change in posture or respiration except in one man whose P-R interval was changed from 0.18 to 0.12 second.

In view of the fact that marked differences can occur in the electrocardiograms of some individuals with change in posture, it is desirable that the position of the patient during the recording of the electrocardiogram should always be noted. It is also suggested that when an electrocardiographic abnormality is found, additional records taken in different positions and phases of respiration may provide further useful information.

SUMMARY

Out of twenty cases with prolonged P-R interval four cases are reported in which definite reduction in the P-R interval occurred on change from the recumbent to the upright position. Similar effects were noted with change in posture and respiration in the electrocardiogram of one man from a group of thirty whose P-R intervals were within the normal limits.

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CONGENITAL HEART DISEASE

CASE REPORTS ON THREE MEMBERS OF A FAMILY

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THIS is a report of congenital heart disease in a mother and two of her children. These cases have been considered worth reporting because no similar report has been found in a careful review of the literature.

CASE REPORTS

CASE 1.—The mother was 34 years old, white, and somewhat obese; her general health had been good. She had had three full-term pregnancies, each with normal delivery and uncomplicated puerperium. At the time of examination she was able to perform her household duties without difficulty. At the age of 18 she first became aware that she had a "heart condition," and that her blood pressure was elevated.

Family History.—The patient has a sister who has three sons, one of whom died at the age of 8 years of congenital heart disease. Another was rejected by the Air Corps because of a "heart condition," and the third son is on limited service in the Army because of a "heart condition and high blood pressure."

Examination.—Blood pressure, left arm, 210/110; right arm, 190/110. The blood pressure was not obtainable in either leg by the usual methods. The femoral, dorsalis pedis, and posterior tibial pulses were not palpable. There were no dilated vessels on the anterior chest wall, and no unusual pulsations were felt. The heart was not enlarged, and the sounds were of good quality. The pulmonic second sound was louder than the aortic second. The rhythm was normal. There was a short, soft, systolic murmur localized at the base of the heart, and a moderately long, high-pitched systolic murmur was localized to the left of the lower end of the sternum. There were no thrills. There was a moderately palpable supra-sternal pulse. There were no signs of decompensation.

Roentgenographic and fluoroscopic examination (Fig. 1) revealed the following: The normal anterior indentation of the esophagus by the aortic knob was not seen after a swallow of barium. This is indicative of hypoplasia of the aorta. The heart size was normal. There was notching of the inferior borders of the ribs posteriorly, between the levels of the fifth through the tenth ribs on the left side, and also a slight degree of notching of the inferior borders of the ribs posteriorly on the right side of the fifth through the ninth ribs.

Laboratory studies, including the electrocardiogram (Fig. 2), were negative.

CASE 2.—The daughter, 9 years old, was first known to have had an abnormal heart at the age of 1½ years, after several attacks of tonsillitis. At the time of examination she presented no complaints, and enjoyed all activities without symptoms of diminished cardiac reserve. Two years previously she had an uneventful tonsillectomy.

Examination.—The blood pressure was 80/50. The apex of the heart was in the fifth intercostal space at the anterior axillary line; the pulmonic second sound was louder than the aortic second; and the rhythm was normal. There was a moderately long, harsh murmur occupying all of systole and part of diastole; this was heard over the entire chest, but was loudest at the base and along the left sternal border. There was a marked thrill in the suprasternal notch. The femoral pulsations were normal. There were no signs of decompensation.

Fluoroscopic and roentgenographic studies (Fig. 3) revealed enlargement of the heart involving all of its chambers, especially the left auricle and right ventricle. There was also some enlargement of pulmonary conus; the aortic knob was not visualized.

The electrocardiogram (Fig. 4) revealed right axis deviation, an inverted T wave in Leads II and IV, and moderate elevation of the R-T segment in Lead III. (Inversion of T, considered normal in children.)

Laboratory investigations, including circulation time (calcium chloride method) and venous pressure, were negative.

CASE 3.—The son, 12 years old, was born a "blue baby," but cyanosis had not been noticed thereafter. At the time of examination he had no complaints; he participated in all activities and showed no evidence of diminished cardiac reserve.

Examination.—Blood pressure, 110/80; the apex beat was felt in the fourth intercostal space, within the midclavicular line; the sounds were of good quality; the pulmonic second was louder than the aortic second; and the rhythm was normal. There was a moderately long, harsh murmur occupying all of systole and part of diastole, heard over the entire chest, but loudest at the base and along the left sternal margin. There was a marked thrill in the suprasternal notch. The femoral pulsations were adequate.

On fluoroscopic and roentgenographic examination of the heart (Fig. 5), slight enlargement of the left auricle and some prominence of the pulmonary conus were noted.*

Laboratory studies, including the electrocardiogram (Fig. 6), circulation time, and venous pressure, were negative.

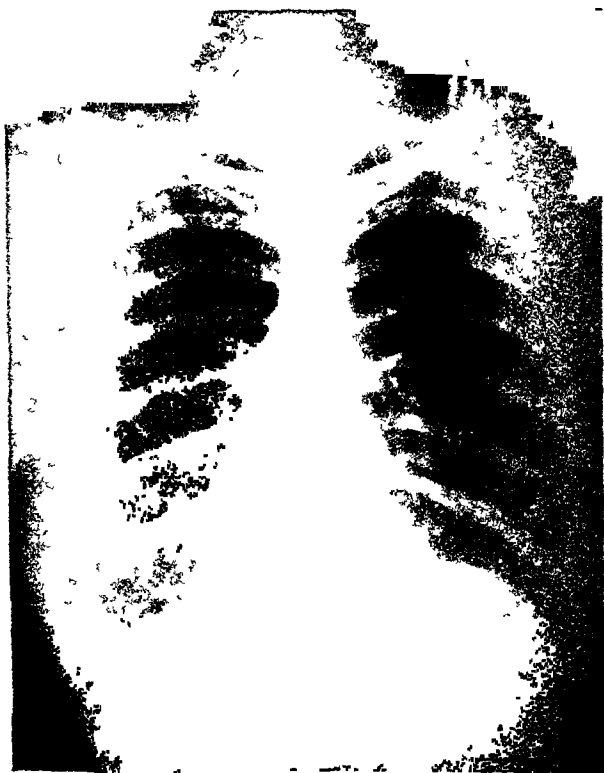


Fig. 1.

Fig. 1.—Mother. (See text for interpretation.)

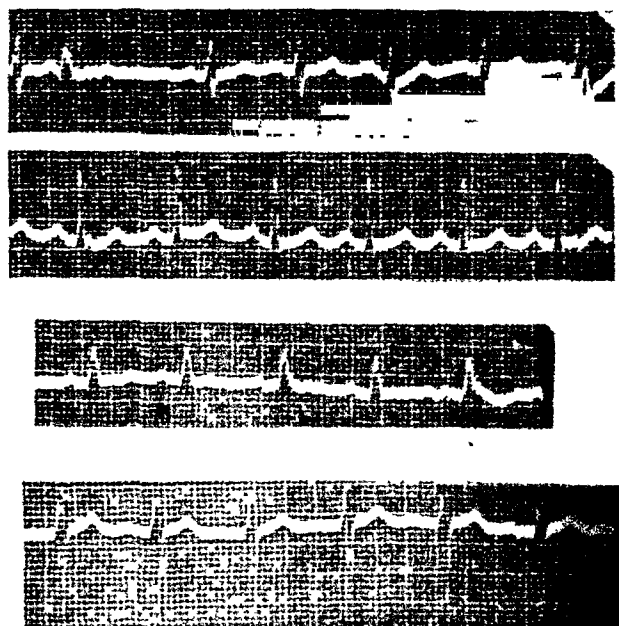


Fig. 2.

Fig. 2.—Mother. Normal electrocardiogram; ventricular premature systole in Lead I.

COMMENT

There have been few reports of congenital heart disease in two members of a family.^{2-4, 6-8} No reports were found in which three members of a family were afflicted. The family herein discussed presents an unusual number of congenital defects. This becomes even more impressive when the mother's sister's family is included. There is the possibility that between four and seven members of these two families were affected.

The three cases which we have reported include one of coarctation of the aorta in the mother, and patency of the ductus arteriosus in the son and daughter. However, another lesion is most likely present also, for patency of the ductus arteriosus does not explain the enlargement of the left and right auricles. A persistently patent foramen ovale can account for enlargement of

*We are indebted to Major Burt Friedman, M.C., for the interpretations of the roentgenologic studies.

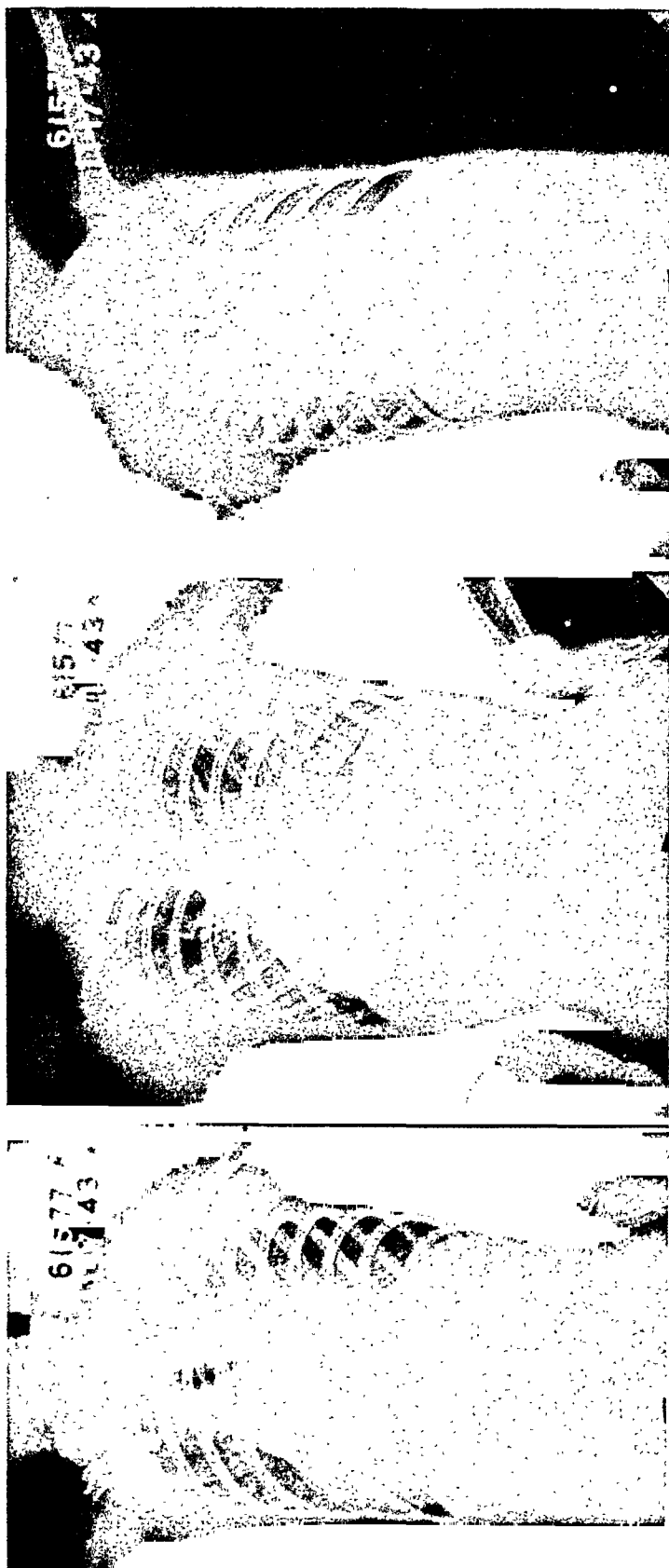


Fig. 3.—Daughter. (See text for description.)

these chambers. In our opinion, the children possess identical lesions, but the daughter has them to a greater degree.

The daughter was the only one to show any degree of cardiac enlargement and an abnormal electrocardiogram (T_2 inverted, indicating myocardial damage). All three, however, were symptom free and apparently were able to carry on their normal daily activities without any difficulty. Although the prognosis must be considered uncertain, it is quite possible that the mother and son may live their full span of years. It is interesting that the mother

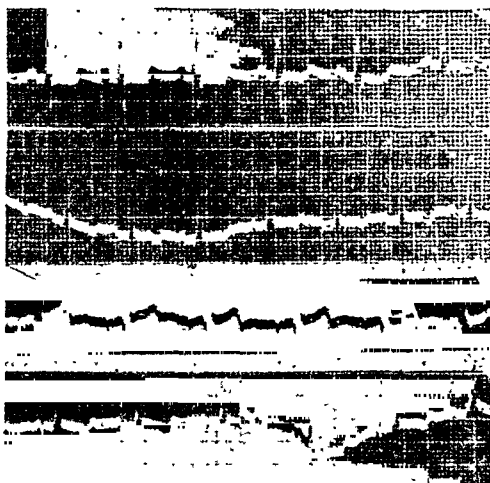


Fig. 4.—Daughter. Note inversion of T wave in Lead II. Right axis deviation.

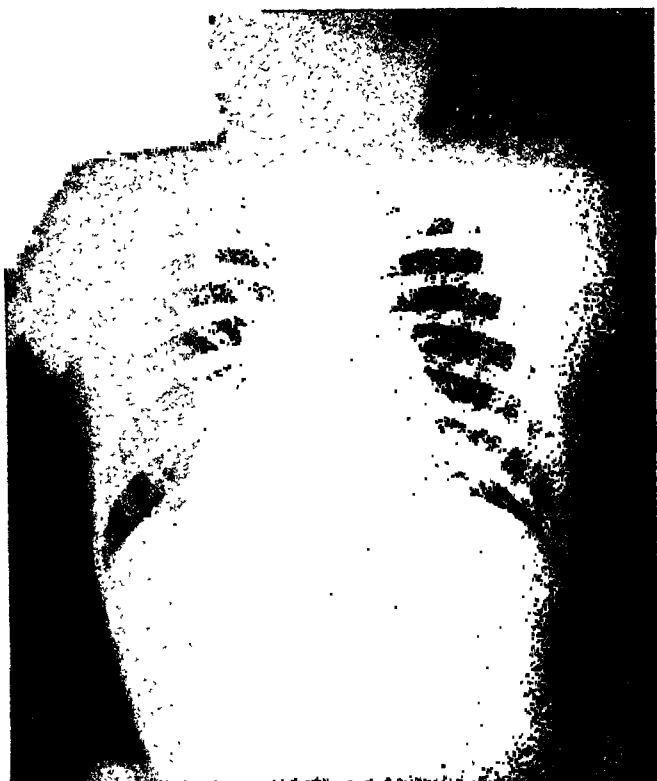


Fig. 5.—Son. (See text for interpretation.)

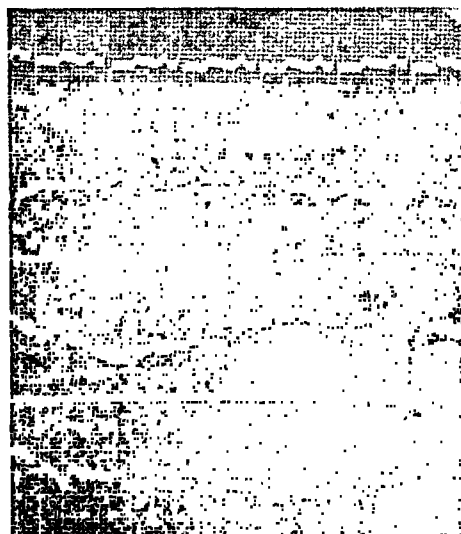


Fig. 6.—Son. Normal electrocardiogram.

went through three pregnancies with normal, spontaneous deliveries. During all of these she never showed any evidence of diminished cardiac reserve. One thus questions the wisdom, at least in this instance, of Walker's recommendation⁵ that the method of choice at the onset of labor in women with coarctation of the aorta is cesarean section.

Maude E. Abbott, in her section, "Congenital Cardiac Disease," in McCrae and Osler's *Modern Medicine*,¹ states that, in a series of 850 cases, there was a

history of congenital defect in either a brother or sister of the patient in only eleven cases.

A discussion of the causes of these congenital malformations must of necessity be extremely speculative. Heredity is probably a factor in only a small proportion of cases, for the high mortality rate of congenital cardiac patients would of necessity prevent any direct transmission of these defects in any considerable numbers. However, this possibility must be given due consideration if the history as given by the mother can be considered reliable. And there is no reason to presume otherwise. The factors involved then would probably lie in the presence of genes of a recessive character. According to Abbott,¹ "The predominating cause of the defect is clearly to be sought in the majority of cases in the environment of the developing embryo." She believes that most are due to the arresting of growth at an early stage, before the various portions of the heart have been formed. But some, particularly those in the more fully developed hearts, may be caused by fetal disease.

CONCLUSION

1. The cases of a mother, son, and daughter with congenital heart disease are reported.

2. The infrequency of such a coincidence is pointed out, and a review of the literature is given.

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STRAIN OF THE PECTORALIS MINOR MUSCLE, AN IMPORTANT CAUSE OF PRECORDIAL PAIN IN SOLDIERS

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IN CIVILIANS, coronary arteriosclerosis is so often responsible for precordial pain that the term angina pectoris has come to be applied chiefly to pain of this origin. At this station, on the other hand, if psychoneurosis and anxiety states were excluded, the most common cause of precordial pain was found to be strain of the pectoralis minor muscle. Over a short period of time eight cases of this condition were observed in the hospital and ten cases in the outpatient department. It is therefore the purpose of this communication to describe a hitherto unrecognized clinical entity and differentiate it from both organic and functional disease of the heart and lungs.

Strain of the pectoralis minor muscle may be confused with intrathoracic and cardiac disease more often when the syndrome occurs on the left than on the right side. The initial complaint is pain in the left or right anterior part of the chest. There may be a history of trauma, but frequently the patient is either unaware of any injury or has forgotten it. The pain in the anterior part of the chest is usually in the midclavicular region at the level of the third, fourth, or fifth ribs, and may radiate to the shoulder along the distribution of the muscle, but never radiates down the arm. It may be intermittent and may appear to be brought on by effort. Analysis, however, will always reveal that the effort involves movement of the affected upper extremity. Tenderness is present throughout the distribution of the pectoralis minor muscle, and is maximal in the midclavicular line at the level of the third, fourth, or fifth ribs. It must be remembered, however, that referred tenderness may be present in angina pectoris and in other diseases involving the thoracic cage. An important diagnostic feature is reproduction of the pain in the left anterior part of the chest by having the patient push the upper arm forward against resistance when the elbow is in any position dorsal to the body. The diagnosis can be established beyond doubt if the injection of procaine into the site of maximal tenderness eliminates the pain. Valuable negative evidence is the absence of signs of intrathoracic disease on physical examination and negative electrocardiographic and roentgenologic observations. In addition, heat, massage, and local rest usually cause the pain to subside within several days. In two of the cases observed, the attacks of pain were recurrent and chronic over a period of years. In one of these cases the strain was produced by lifting a dipper full of molten iron, and, in the other, by a fall from a horse.

REPORT OF A TYPICAL CASE

A private, 28 years old, was admitted to the Station Hospital complaining of precordial pain of two days' duration. This pain was in the left anterior part of the chest in the midclavicular region, and radiated to the left shoulder. It was intermittent and apparently brought on by effort. On further questioning, the effort consisted of lifting heavy objects and certain physical exercises in which the left upper extremity was used. In addition, the pain was aggravated by coughing, sneezing, or deep inspiration. There was no

pain between attacks, although a sense of soreness persisted. No information relevant to the patient's chief complaint was elicited from the past or family history.

On physical examination, tenderness was present in the left anterior part of the chest along the distribution of the left pectoralis minor muscle, and was maximal at the level of the fourth and fifth ribs in the midclavicular line. Bringing the left elbow across the chest toward the right shoulder against resistance did not elicit the pain despite obvious tension produced in the lower portion of the left pectoralis major muscle. When the left elbow was dorsal to the body either above, at a level with, or below the left shoulder, movement of the arm forward against resistance reproduced the left anterior chest pain. Injection of procaine into the site of maximal tenderness in the left anterior part of the chest eliminated the pain completely for several hours and permitted free movement of the left arm without pain in any position. The blood cell count, sedimentation rate, and urine examination, as well as the electrocardiogram and chest roentgenogram, revealed no significant abnormalities.

The patient was kept at rest in bed, and the left pectoral region was subjected to diathermy and gentle massage twice a day. One week after admission he was returned to duty completely free of pain and tenderness.

Since the pectoralis minor muscle has its origin in the midclavicular region of the chest at the level of the third, fourth, and fifth ribs, whereas the pectoralis major originates along the entire parasternal region, this syndrome is probably caused by rupture of a variable number of the fibers of the pectoralis minor from their site of origin on the chest wall, rather than by any injury to the pectoralis major. This is further substantiated by absence of a visible defect or subcutaneous hemorrhage, features usually present in such cases of rupture of the pectoralis major as are described.¹⁻³ In addition, tension produced in the lower pectoralis major by bringing the arm across the chest fails to reproduce the pain, whereas pushing the arm forward against resistance from a position dorsal to the body, thus bringing the shoulder down and forward, a maneuver effected in part by contraction of the pectoralis minor,⁴ does reproduce the pain. Only one case⁵ of rupture of the pectoralis minor has been recorded. In this case there was apparently a complete avulsion of the muscle, with the production of a persistent tumor in the pectoral region. In the cases reported in this communication there was a lesser degree of muscle injury more properly called "strain."

Pectoralis minor muscle strain is more common in soldiers than civilians, probably because of the strenuous nature of certain military duties and also because most soldiers are required to participate in calisthenics. This type of strain should therefore be kept in mind, especially in the Armed Forces, whenever a patient complains of left or right anterior chest pain, whether or not it is possible to elicit a history of trauma. It should never be confused with disease of the heart or lungs, or attributed to a psychoneurosis or to "goldbricking." Although several authors have emphasized the importance of distinguishing angina pectoris from muscle strain^{6,7} and from "fibrositis" of the chest wall,⁸ none seem to be aware of the specific clinical entity of pectoralis minor muscle strain. This diagnosis may be verified by the simple measures here reported.

SUMMARY

1. Pectoralis minor muscle strain is a common cause of precordial pain in soldiers.

2. Its hitherto undescribed clinical features are discussed and differentiated from organic and functional disease of the heart and lungs.

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ORAL SINGLE-DOSE DIGITALIZATION WITH DIGITALIS LEAF AND DIGITALINE "NATIVELE"

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WITH THE COLLABORATION OF H. N. GINSBURG, M.D., I. SCHIFF, M.D., AND
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IN A series of reports¹⁻⁶ Gold and Cattell and their associates have shown the inadequacy of applying animal assays to man when comparing potency or toxicity of different types of digitalis drugs. A method was developed by them for comparing such drugs in humans by noting the effect upon the S-T-T complex in the electrocardiograms of patients with sinus rhythm, or by determining the degree of slowing of the average resting ventricular rate in patients with persistent auricular fibrillation. They found that an average digitalizing effect was obtained in a few hours when either 15 cat units of U.S.P XI digitalis leaf or 1.2 mg. (3 cat units) of digitaline "Nativele" were administered as a single dose to patients who had been without any digitalis drug for several weeks; digitalization was obtained with the same dosage of "Nativele" intravenously as orally. Toxic effects were of the same nature with both drugs; however, with "Nativele" approximately 2 per cent of the cases showed toxic effects due to local action, and a similar number showed toxic effects due to systemic action when doses of 1.2 mg. were used; while with digitalis about 20 per cent showed toxic effects due to local action, and about 4 per cent showed toxic effects due to systemic action.⁴ When 2 mg. of "Nativele" were used, the incidence of toxicity was much higher than when doses of 1.2 mg. were used.⁶

Digitaline "Nativele"* is a commercial preparation from *Digitalis purpurea*, considered to contain at least 90 per cent of crystalline digitoxin and to be fairly completely absorbed from the intestine in man.^{4, 5}

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*For a discussion of the nomenclature and relation to commercial digitoxin see Gold, Kwit, and Cattell¹ and Gold, Cattell, and associates.⁶

TABLE I

CASE	PA-TIENT	AGE (YRS.)	SEX	WEIGHT (POUNDS)	DIAGNOSIS	HEART FAILURE	DRUGS GIVEN
1	RS	40	F	100	Rheumatic heart disease, mitral stenosis and insufficiency	Mild	N-D-N
2	JW	44	M	140	Rheumatic heart disease, mitral stenosis and insufficiency	0	N-D-N
3	MH	58	F	130	Rheumatic heart disease, mitral stenosis and insufficiency, aortic insufficiency	Mod. severe	N-D-N
4	ND	68	M	225	Arteriosclerotic heart disease	0	N-D-N
5	MZ	59	F	125	Rheumatic heart disease, mitral stenosis and insufficiency	0	N-D-N
6	SS	29	M	145	Rheumatic heart disease, mitral stenosis and insufficiency	0	N-D-N
7	GL	37	M	180	Rheumatic heart disease, mitral stenosis and insufficiency	0	N-D-N*
8	EF	52	F	110	Rheumatic heart disease, mitral stenosis	0	N-D
9	FD	59	F	125	Arteriosclerotic heart disease	0	N-D-N
10	JO	60	M	155	Arteriosclerotic heart disease	0	N-D-N
11	LS	53	F	100	Rheumatic heart disease, mitral stenosis and insufficiency, aortic insufficiency	Severe	N-D
12	SC	57	F	260	Arteriosclerotic heart disease	0	N-D-N
13	FW	32	M	175	Rheumatic heart disease, mitral stenosis and insufficiency, aortic insufficiency	Severe	N
14	LD	58	F	155	Arteriosclerotic heart disease	Mod. severe	N
15	JF	37	M	148	Rheumatic heart disease, mitral stenosis and insufficiency	0	N-N*

N = Digitaline "Nativelle" orally (1.2 mg.).

D = Digitalis orally (Digitora, ten tablets, each containing 1.28 grains of U.S.P. XII digitalis leaf).

N* = Digitaline "Nativelle" intravenously (1.2 mg.).

The present study was undertaken to confirm for ourselves the safety and comparative efficacy of administering digitalis leaf* and "Nativelle" in single digitalizing doses. Fifteen patients with chronic auricular fibrillation were used in the study (Table I). Of these, all but Patients 8, 11, 13, 14, and 15 received "Nativelle" twice and digitalis once (1.2 mg. of the former and 12.8 grains of the latter). Patients 8 and 11 received "Nativelle" once and digitalis once. Patients 13, 14, and 15 received "Nativelle" only; the last received it once orally and once intravenously; the other two received it only once orally. One of the two "Nativelle" administrations of Patient 7 was made intravenously.

All the patients were kept on a salt-poor diet in the hospital and were ambulatory except for those in severe heart failure. The heart rate was measured daily, for at least a full minute, after twenty minutes or longer of complete rest in bed. When maintenance of an elevated heart rate level indicated fairly complete elimination of previous digitalis drug and acclimatization to the hospital environment, each patient was given the "Nativelle" and kept in bed that day; the heart rate was measured hourly for twelve hours, after which the patient was permitted up and about and daily heart rates were then taken until (in thirteen cases) a new level was reached and maintained before starting upon further therapy.

RESULTS

Oral Administration.—The initial control levels of heart rate prior to the administration of drug ranged from 82 to 159 beats per minute, in most in-

*The preparation of digitalis used was Upjohn "Digitora," of which the "1½ Digitalis Strength" tablet contains 1.28 grains of U.S.P. XII digitalis leaf, equal to 1 cat unit or 0.83 U.S.P. XII Digitalis Units. Ten such tablets comprised the single dose used in all cases.

stances falling below 110. The heart rate levels just prior to administration of the digitalis drugs in those cases receiving two or three courses were for the most part of the same order, so that it was possible to compare the effects of the several courses. The heart rate curves obtained following medication were essentially similar to those obtained under like circumstances by Gold and Cattell and their co-workers both as to amount and time of change. In the patients who had "Nativele" twice, the two curves were nearly identical, and the whole-leaf digitalis effect was also very much the same (Figs. 1 and 2). The main difference observed was that digitalis leaf tended to depress the rate somewhat more than "Nativele," and the rate tended to remain low longer and be more delayed in returning to its control level (Fig. 2).

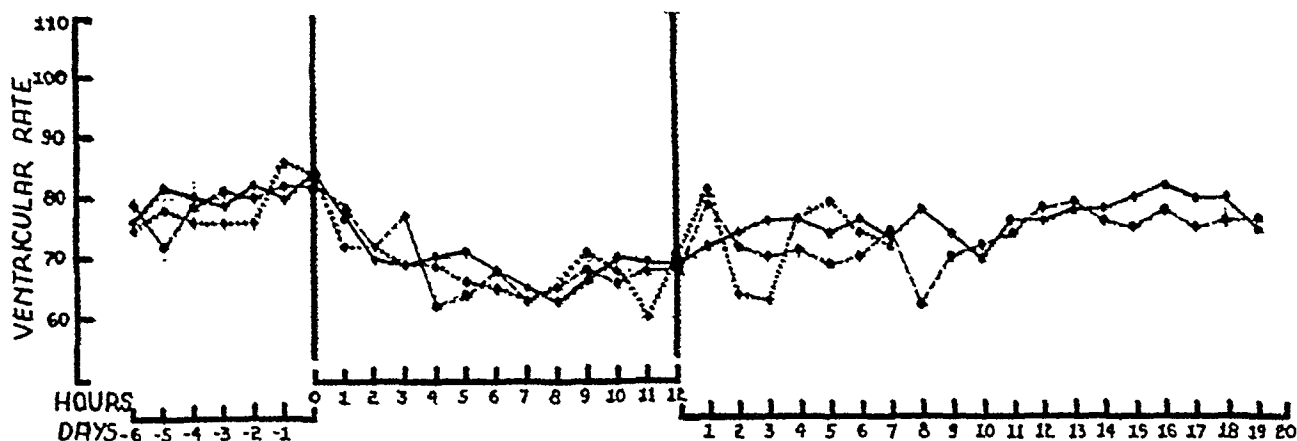


Fig. 1.—Chart listing pertinent data on Patient 4, with arteriosclerotic heart disease, persistent auricular fibrillation, and no heart failure. This patient received at time 0, on different occasions, first, 1.2 mg. of digitaline "Nativele" (solid-line curve), then 12.8 grains digitalis (dash curve), and then again 1.2 mg. "Nativele" (dot curve), each in a single oral dose. No difference is seen between the effect of "Nativele" and digitalis administrations. The heart rate fell from a range of about 83 in about seven hours to a level of about 65, and returned to the control range in about twelve days. Ventricular rate is in beats per minute. Discussed in text.

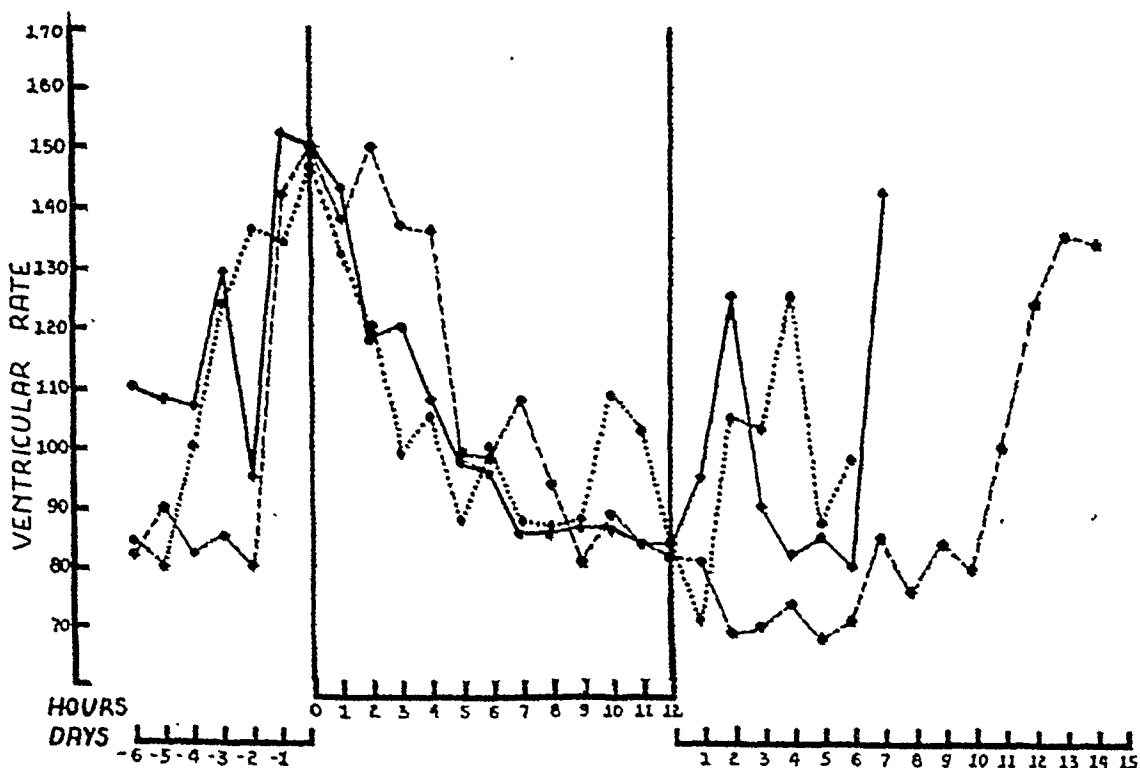


Fig. 2.—Chart listing pertinent data on Patient 6, with rheumatic heart disease, mitral stenosis and insufficiency, persistent auricular fibrillation, and no heart failure. This patient received the same three courses as Patient 4 (Fig. 1) and in the same sequence (conventions as in Fig. 1). Both "Nativele" and digitalis depressed the rate in five to eight hours from a range of about 150 to one of about 85. With "Nativele" the heart rate tended to return towards the control level in a few days; with digitalis it remained depressed (even reaching a range of 70 for a few days) for ten days and returned to the control range in twelve days. Discussed in text.

TABLE II

(1) EXPERI- MENT	(2) CONTROL LEVEL (BEATS/ MIN.)	(3) LOW LEVEL (BEATS/ MIN.)	(4) DECLINE (BEATS/ MIN.)	(5) PER CENT DECLINE (%)	(6) TIME TO REACH LOW LEVEL (HRS.)	(7) LEVEL OF 1/2 DECLINE (BEATS/ MIN.)	(8) TIME TO REACH 1/2 DECLINE (HRS.)	(9) TIME TO RETURN TO CONTROL LEVEL (DAYS)
<i>Essential Data on Heart Rate of Twenty-Four Cases of Oral "Nativelle"</i>								
1	124	80	44	35	7	102	3	10
1	122	67	55	45	7	95	2	-
2	99	73	26	26	5	86	2	11
2	97	70	27	28	5	83	2	-
3	108	72	36	33	9 1/2	90	2 1/2	19
3	88	66	22	25	8	77	2 1/2	9
4	84	63	21	25	7	74	1 1/2	16
4	84	63	26	23	7	101	1	-
5	114	88	26	23	7	101	2	11
5	118	90	28	24	8	104	4	-
6	150	86	64	43	7	118	2	8
6	147	87	60	41	7	117	2 1/2	-
7	89	55	34	38	5	72	2	7
8	94	90	4	4	6	92	2	-
9	100	70	30	30	7	85	3	13
9	92	70	22	35	8	86	3	-
10	102	74	28	27	7	88	4	10
10	97	75	22	23	8	86	3	-
11	91	73	18	20	7	82	3 1/2	-
12	96	80	16	17	7	88	2	16
12	91	75	16	18	6	83	3	7
13	105	66	39	37	10	86	4 1/2	-
14	130	73	57	44	10	101	3	-
15	114	71	43	38	4	92	3	10
Average	106	74	32	29	7	90	2 1/2	11
<i>Essential Data on Heart Rate of Two Cases of Intravenous "Nativelle"</i>								
7	89	52	34	38	4	68	1	-
15	96	56	40	42	10	76	1 1/2	-
<i>Essential Data on Heart Rate of Twelve Cases of Oral Digitalis</i>								
1	159	78	81	51	7	118	2 1/2	14
2	90	63	33	37	7	76	1 1/2	15
3	98	60	38	39	6	79	2	20
4	82	64	18	22	4	73	2	21
5	95	55	40	42	10	75	1	31
6	150	85	65	43	9	117	4 1/2	12
7	87	44	43	50	6	66	1 1/2	-
8	101	94	7	7	5	97	3	-
9	94	66	28	33	8	80	2	13
10	93	64	29	31	8	79	2 1/2	13
11	120	90	30	25	6	105	4 1/2	-
12	85	68	17	20	5	76	3	20
Average	104	69	36	33	7	87	2 1/2	18

The figures in this table are obtained by inspection of the curves and are rough approximations based upon the trends of these curves.

In twenty-four trials with "Nativelle" orally (Table II), the rate fell from a level of 84 to 150 (average, 106) in four to ten hours (average, 7) to a level of 55 to 90 (mostly 60 to 80; average, 74), representing a fall in most cases of 15 to 45 per cent (average, 29 per cent). Half the fall occurred in one to four and one-half hours (average, two and one-half hours). The control level was reached again in seven to nineteen (average, eleven) days.

The effects with digitalis leaf were of the same order. In twelve trials with digitalis (Table II) the rate fell from a level of 85 to 159 (average, 104) in four to ten hours (average, seven) to a level of 44 to 94 (average, 69), a fall in most cases of 20 to 40 per cent (average, 33 per cent). Half the fall occurred in one to four and one-half hours (average, two and one-half hours). The control level was reached again in twelve to twenty-one (average, eighteen) days.

While it is important to appreciate the existence of individual variations in response, a composite curve better illustrates the average effect. To accomplish this, the twelve cases which received both drugs were used. The "Nativele" rates at each time period were first averaged in those cases receiving "Nativele" twice, then averages of the twelve cases were obtained and plotted as a single curve; the digitalis points were similarly averaged and plotted (Fig. 3). Examination of the curves of averages in this figure shows no essential difference for the first four hours; thereafter, the average rate was somewhat lower with digitalis. The rate remained low for about a week with digitalis, while with "Nativele" the rate began slowly to rise again after the first day.

Fig. 4 compares the percentage decline in the individual cases. It shows that the decline was greater with digitalis than with "Nativele" in eleven of the twelve cases.

With both drugs, scatter graphs from data in Table I showed a rough linear trend when the initial level of heart rate (column 2) was plotted against

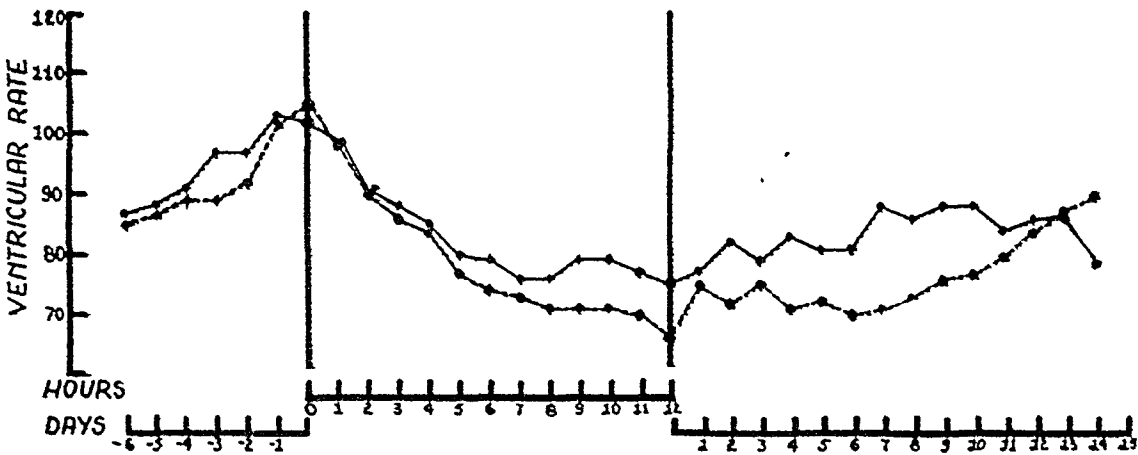


Fig. 3.—Chart showing average heart rates for "Nativele" (solid-line curve) and for digitalis (dash curve) in the twelve patients receiving both drugs. Discussed in text.

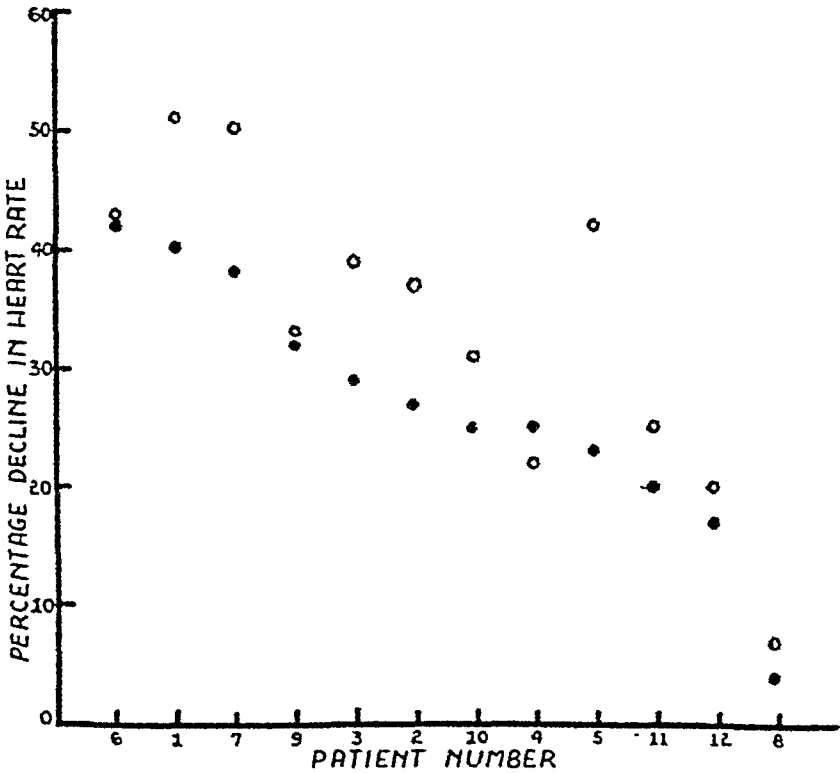


Fig. 4.—Chart showing the percentage decline in heart rate with "Nativele" (solid circles) and digitalis (open circles) in each of the twelve cases receiving both drugs. The "Nativele" points in those cases receiving that drug twice are an average of the two courses. Discussed in text.

its low level (column 3), the degree of decline (column 4) and the percentage decline (column 5), respectively. The best trend was obtained in the graph of initial heart rate level plotted against the degree of decline in heart rate. The low level reached tended to be at a faster rate and the actual and percentage decline in heart rate tended to be greater, the greater the initial heart rate. This effect was valuable in that, when initially high, the heart rate tended to reach normal; when low, there was less tendency to decline and go below normal.

Examination of columns 2, 4, 5, 8, and 9 of Table I shows that there is no apparent relationship between the initial level or degree of decline in heart rate, and the time necessary to reach the low level or to return to the control level.

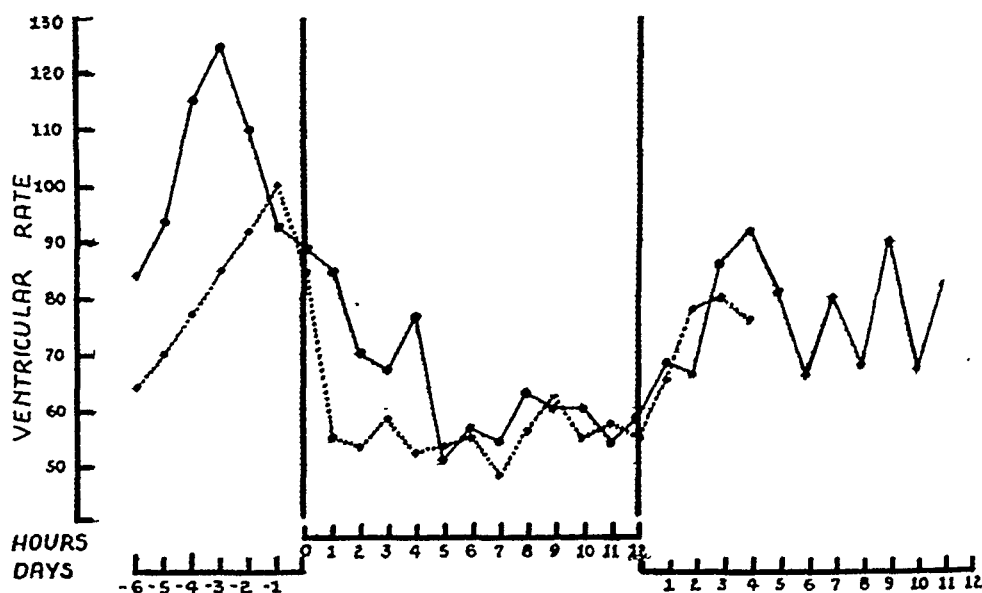


Fig. 5.—Chart listing pertinent data on Patient 7, with rheumatic heart disease, mitral stenosis and insufficiency, persistent auricular fibrillation, and no heart failure. This patient received 1.2 mg. "Nativelle" orally (solid-line curve), then digitalis (not shown), and later 1.2 mg. "Nativelle" intravenously (dot curve). Oral "Nativelle" reduced the heart rate from 89 to a range of 55 in five hours; intravenous "Nativelle" reduced the rate from 84 to the same range in one hour; after five hours the curves were essentially the same. Discussed in text.

Intravenous "Nativelle."—In two cases, the effects of oral and intravenous administration of the same 1.2 mg. dose of "Nativelle" were compared in the same patient. One such experiment is illustrated in Fig. 5. In both cases the initial decline was more rapid than usually occurred with oral "Nativelle." However, after the first three or four hours, the curves were much the same for both intravenous and oral "Nativelle." This is in accord with the observations of Gold and Cattell and their associates.

Toxicity.—In only one of the twenty-six instances was "Nativelle" administration associated with a definite toxic effect; in this instance spotty amblyopia occurred at the second hour. There was also one instance of transitory aching left chest pain at the third hour and one of slight upper abdominal heaviness with belching at the fourth hour. The patient with amblyopia also had a constricting feeling about the chest and a sensation of vigorous heart action during the fifth and sixth hours.

In two of twelve instances (Patients 1 and 11), digitalis leaf administration was associated with vomiting, occurring at the twentieth and twenty-fifth minutes, respectively, and in one of these it occurred again at the second and third hours; however, both patients had nausea and vomiting prior to the admin-

istration of the drug. Both, in spite of the early vomiting, showed a satisfactory reduction in heart rate. One patient had dizziness at the first hour and nausea at the eighth hour, while another had abdominal cramps at the ninth hour.

This incidence of toxic manifestations would appear to be of the same order as that observed by Gold and Cattell and their associates, with similar dosages.

DISCUSSION

Our experience, meager when compared to the large experience of Gold and Cattell and their group, has led us to the following conclusions, which are, in most respects, similar to theirs⁶:

1. Both digitaline "Nativelle" in 1.2 mg. dosage and digitalis leaf in 12.8 grain U.S.P. XII dosage would appear to provide safe, effective, single-dose digitalization in *undigitalized* patients.

2. "Nativelle" has a lower incidence of toxic effects.

3. Intravenous administration of "Nativelle" possesses little advantage over the oral route.

In addition to the above series, about fifteen patients in cardiac failure, most of them without auricular fibrillation, were given 1.2 mg. of digitaline "Nativelle" with good clinical results and no toxic effects. It was sometimes necessary to follow up with further smaller doses before an adequate digitalizing effect was obtained.

From our experience it would appear that single massive oral dosage may be safer than generally realized hitherto, provided *always* that the patient has not had digitalis in the past two or three weeks. Intravenous digitaline "Nativelle" is not the method of choice in these cases, since all the benefits of intravenous use of this drug can be obtained orally. Single dose administration is not advocated as a substitute for intravenous digitalization in cardiovascular emergencies; in such cases strophanthin K or ouabain are the drugs of choice since these drugs act more rapidly than digitaline "Nativelle." However, when an effect is desired in a few hours, the effect can more safely be accomplished by large oral doses rather than by intravenous administration of digitalis preparations. This is the place for single large-dose administration of digitalis.

Even when a moderately rapid effect is desired, we do not advocate single large-dose oral administration as a general rule. In most cases it would be preferable to give the drug in divided doses, such as 0.8 mg. of digitaline "Nativelle" followed by 0.4 mg. in six to eight hours and by such subsequent doses as might be necessary to attain the desired effect. When digitalized, the patient may be maintained on digitalis leaf, "Nativelle," or some other preparation. Average maintenance doses of "Nativelle" are 0.1 to 0.2 mg. daily, more usually the latter.⁶

The similarity of intravenous and oral digitalizing dosage of "Nativelle" is not found with any other digitalis type of preparation; Lanatosid C, for example, requires about ten times as much drug orally as intravenously for rapid digitalization.² This, plus the fact that a digitalizing effect is obtained about as rapidly in most cases with oral as with intravenous "Nativelle," suggests that the drug, given orally, is fairly rapidly as well as fairly completely absorbed.

The significant difference found in the time necessary for the heart rate to return to a level range, averaging eighteen days with digitalis and eleven with "Nativelle," and the tendency of the heart rate to retain a low level longer with

digitalis than with "Nativelle" indicate a more rapid excretion or destruction of "Nativelle" than of digitalis leaf.

The actually greater degree of the average depression of heart rate with digitalis than with "Nativelle" is apparently due to the dosage. Thus, Gold and Cattell and their co-workers³ demonstrated in their time graphs that a greater depression of heart rate occurs with the larger dosage of digitalis when two different doses are compared in the same patient. It would, therefore, appear that 1.2 mg. of digitaline "Nativelle" is equal in potency to somewhat less than 12.8 grains of U.S.P. XII digitalis of the preparation used in our study. This does not agree with the experience of Gold and Cattell and their associates⁶ who by the same method, found 1.2 mg. of "Nativelle" approximately equal in potency to 18.5 grains of U.S.P. XII digitalis leaf. The difference may be in the digitalis leaf preparation employed in the two studies.

SUMMARY AND CONCLUSIONS

In order to verify the safety and efficacy of single-dose digitalization and to compare digitalis leaf and digitaline "Nativelle" in this respect, the effects upon the resting heart rate of twelve oral administrations of 12.8 grains of U.S.P. XII digitalis leaf and twenty-four oral and two intravenous administrations of 1.2 mg. of digitalis "Nativelle" were studied in fifteen patients with persistent auricular fibrillation after the manner of Gold and Cattell and their associates.

All administrations had essentially similar effects, causing an average fall in heart rate of about 30 per cent in four to ten (average, seven) hours. Digitalis leaf, in the dosage used, tended to depress the rate somewhat more than "Nativelle" did, and the return to control level was more delayed, averaging eighteen days as compared to eleven days with "Nativelle." With both drugs a greater actual and percentage decline in heart rate tended to occur with greater initial heart rate.

Intravenous "Nativelle" in the two cases where it was used, caused a more rapid decline in rate than oral "Nativelle" but after three to four hours its effect was much the same as that of oral "Nativelle" in the same dosage.

The incidence of toxic manifestations appeared, in this small series, to be of the same order as that observed by Gold and Cattell and their co-workers in a larger series and was less with "Nativelle" than with digitalis leaf.

Either drug in the dosage used would appear to provide a safe, oral, single-dose digitalization, and might be useful when an effect is desired in a few hours in undigitalized patients. This is, in general, preferable to intravenous administration, except in cardiovascular emergencies, where a *Strophanthus* derivate, given intravenously, is preferable for its more rapid effect. While single-dose digitalization was used experimentally, and sometimes therapeutically, divided dosage, such as 0.8 mg. of "Nativelle" followed by 0.4 mg. in six to eight hours, would be preferable in most cases.

The similarity of intravenous and oral digitalizing dose of "Nativelle," found with no other digitalis type of preparation, suggests that the drug, given orally, is fairly rapidly as well as fairly completely absorbed. It would also appear that "Nativelle" is probably more rapidly excreted or destroyed than digitalis leaf.

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CARDIAC ANEURYSM WITH RUPTURE

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ALTHOUGH many cases of cardiac aneurysm have been reported, rupture of aneurysm of the heart as a cause of death is exceedingly rare. Death in this condition is usually due to the underlying heart trouble, such as coronary disease or myocarditis. A case of tuberculous myocardiac aneurysm with rupture has been reported by Jones and Tilden,¹ and a mycotic aneurysm of the heart with rupture has been described by Pirani.² Gross and Schwedel³ reported forty-three cases without an instance of rupture, and Hunter and Benson,⁴ in forty cases of spontaneous rupture of the heart, found only one instance in which an aneurysm was the cause. Thomas,⁵ in 1930, reported a single case of rupture of aneurysm of the heart. Of fifteen cases of cardiac aneurysm reported by Parkinson, Bedford, and Thomson,⁶ none of the seven who died experienced rupture of same. In twenty-one cases reported by Brams and Gropper,⁷ rupture did not occur. Friedman and White¹⁸ found no instance of ruptured cardiac aneurysm among 165 cases of chronic or healed myocardial infarction.

Aneurysm of the heart is rarely recognized during life. Brams and Gropper⁷ made a clinical diagnosis in only four out of twenty-one cases, and in these four cases the evidence was not positive. Only three of the fifteen cases reported by Parkinson, et al.⁶ were discovered before autopsy. Dressler and Pfeiffer⁸ reported ten cases in which the condition was perceived during life. Up to 1914 only three cases were correctly diagnosed clinically. Sternberg,⁹ Lutembacher,¹⁰ and Christian and Frick,¹¹ as late as 1939, felt it was difficult if not impossible to diagnose cardiac aneurysm during life.

Nearly all cases are preceded by myocardial infarction due to coronary disease. The resulting fibrosis leaves a weak spot in the heart wall which dilates with the increase of intraventricular pressure. Aneurysm may also occur from abscess of the heart wall, trauma, ulcerative lesions of bacterial endocarditis, or congenital defects (Fulton¹²).

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Working with dogs, Sutton and Davis¹³ showed that with adequate rest a much firmer scar was formed after experimental infarction, and the tendency to aneurysm was correspondingly much less than in dogs who did not have the proper rest. They, therefore, felt that adequate rest after coronary thrombosis was of value in preventing the formation of an aneurysm of the heart.

The symptoms and signs may be grouped under (1) clinical, (2) electrocardiographic, and (3) roentgenographic; the latter of which is the most important. There is usually a previous history suggesting coronary thrombosis with infarction. Among the presumptive signs that have been described are enlargement of the heart to percussion; a diffuse and increased area of cardiac impulse, often measuring 7 to 9 cm., with the pulsation more marked between the apex and the sternum than at the apex proper; a small pulse with elevation of intercostal spaces; a systolic murmur just inside the apex; a heavy cardiac thrust associated with a feeble pulse; a wavy pulsation along the inside of the left nipple; gallop rhythm; and a continuous rather severe pain limited to a well-defined area, described by Lutembacher.¹⁰

According to Brams and Gropper,⁷ electrocardiographic studies are of no direct diagnostic aid as they show only the antecedent coronary thrombosis. Several electrocardiographic patterns have been described. Eliaser and Konigsberg,¹⁴ in reviewing five of their own cases and previously published cases of aneurysm of the left ventricle following coronary occlusion, with electrocardiographic studies, found in 27.3 per cent a downwardly directed major deflection in Lead I, with inversion of the T wave and upright P wave, and an upright ventricular complex in Lead III. In 36.4 per cent of these cases the ventricular complexes were directly downwardly in Leads II and III with an upright major deflection in Lead I of either normal or low amplitude. In 18.2 per cent of the cases left bundle branch block was present. Nordenfelt¹⁵ reported the following electrocardiographic characteristics in large chronic aneurysms of the anterior wall of the left ventricle: relatively low R_1 , deep S_2 and S_3 , elevated S-T segments in all leads, negative T_1 , and positive T_2 and T_3 . In four cases in which Lead IVF was recorded, R was absent, S was deep, and the S-T segment was elevated with a positive T wave. He feels that if these changes persist over a long period of time, aneurysms or extensive fibrosis of the anterior wall of the left ventricle may be suspected in cases where there is a preceding history of anterior infarction. Thirteen out of fifteen cases reported by Parkinson and his associates⁶ showed a T_1 type of infarction, and one showed the T_3 type. In the Dressler and Pfeiffer⁸ groups, all cases showed electrocardiographic signs of previous infarction, and deep S deflections in Leads II and III were noted in half of them. In a third of his cases Master¹⁷ found a combination of intraventricular block with a deep Q wave and inverted T wave in Lead I, which he felt suggested the diagnosis of cardiac aneurysm.

The following roentgenographic findings have been described: a circumscribed bulging of the left border of the cardiac silhouette with systolic lateral pulsation; discrepancy between an enlarged left ventricle and a small vascular pedicle (Parkinson, et al.⁶); a broadening of the apex of the heart giving it a square or rectangular appearance; an elongation of the heart to the left; calcification of the aneurysmal sac; evidence of adhesion between the heart and chest wall or diaphragm; and abnormal or absent pulsation of the aneurysmal zone. Aneurysms of the posterior wall of the ventricle are best seen in the left oblique position and may cause a visible displacement of the esophagus. Anterior aneurysms are best seen in the right oblique position. Ledging of the

anterior heart border is of great diagnostic value (Parkinson, et al.⁹). Fluoroscopy may reveal a bulge which is not seen in the roentgenogram. A distention of the anterior wall of the left ventricle, chiefly toward the right, will result in a displacement of the anterior longitudinal sulcus and of the right ventricle. Roentgenkymographic studies may show an aortic type of pulsation along the outer border of the left ventricle (Browne and McHardy¹⁶). It is very difficult to recognize roentgenologically an aneurysm situated in the apex as it may be buried in the left hepatic lobe or obscured by the diaphragm. This is unfortunate since the apex is the most frequent location for cardiac aneurysms.

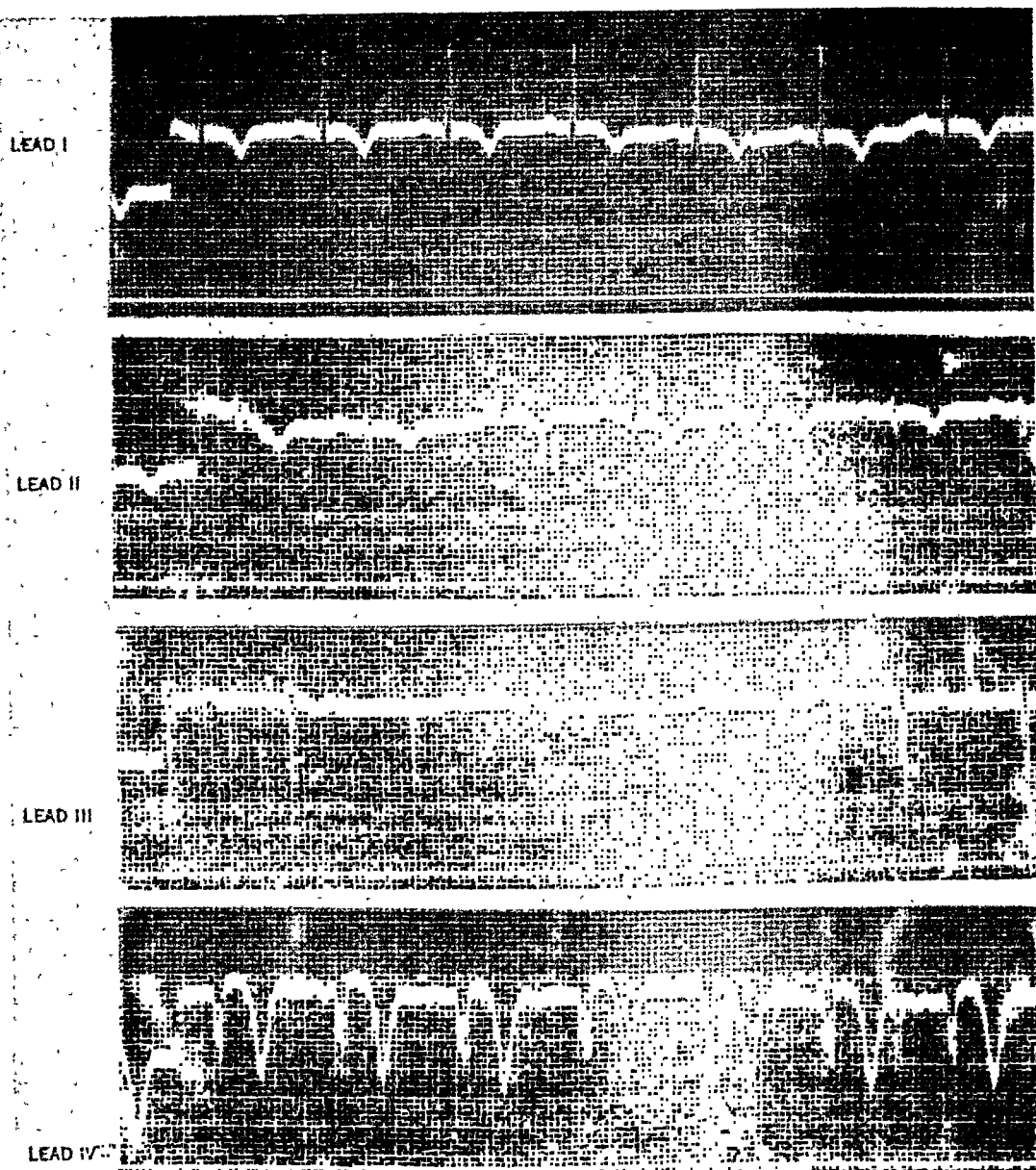


Fig. 1.—Electrocardiogram taken during first admission, showing sharply inverted T waves in Leads I, II, and IV F with major deflections of the QRS complexes directed downwardly in Leads II, III, and IVF; and a marked increase in amplitude of T wave and absent R wave in Lead IVF.

CASE REPORT

A 67-year-old white man stated he was perfectly well until ten days previous to his first admission to the hospital on Feb. 16, 1944. On this day, while shaving, he was suddenly seized with a sharp, severe, precordial pain which forced him to lie down. About one-half hour later he began to vomit and continued to do so intermittently for six hours. There was no previous history of pain in the chest. There was no earlier record of shortness of breath, palpitation, or chronic cough.

Examination revealed an elderly, white man lying quietly in bed. The heart was markedly enlarged both to right and left; the roentgenogram showed its greatest transverse diameter to measure 17 cm. as compared with an internal thoracic diameter of 32 centimeters.

There was a soft systolic murmur at the apex, A_2 was greater than P_2 , and the first apical sound was rather distant. The heart rate was 76 per minute, and the rhythm was normal. There was marked dilatation of the aorta. The blood pressure was 134/74. There was sclerosis of the retinal arteries. The prostate gland was slightly enlarged. Otherwise the general physical examination was not remarkable.

At this time the leucocytes numbered 5,200, and the sedimentation rate was 16 mm. in one hour. The Kline test was negative. Electrocardiogram (Fig. 1) was interpreted as evidence of fairly recent previous anterior myocardial infarction with deep S_2 and S_3 waves. The final diagnoses were as follows: generalized arteriosclerotic heart disease with coronary thrombosis and recent anterior infarct; moderate prostatic hypertrophy.

The patient was kept in bed for about four weeks and then gradually was allowed very restricted activity.



Fig. 2.—Roentgenogram of chest (mobile unit), showing markedly enlarged heart and densities in both lung bases.

He was next seen on April 29, 1944, complaining of a moderate productive cough; spells of pain beginning in the upper abdomen and radiating to the precordial region, accompanied by shortness of breath. At this time the heart was enlarged to the left anterior axillary line. The tones were faint; heart rate was regular, 130 per minute; and the blood pressure was 160/96. There was nothing distinctive about the cardiac pulsations. Moist râles were present at both pulmonary bases with some dullness at the right base. The abdomen was distended, but the liver was not palpable. There was no edema of the extremities.

In the portable x-ray of the chest (Fig. 2) the cardiac borders were difficult to visualize, and the size of the heart was hard to estimate because of the short focal distance. However, there was a bulging of the cardiac apex far to the left. The lung fields had the appearance of extensive pulmonary edema.

Electrocardiogram (Fig. 3) taken on the second day of this admission revealed old anterior myocardial infarction with marked left ventricular preponderance.

Clinical diagnoses were: old arteriosclerotic heart disease with old anterior infarction; generalized arteriosclerosis; benign prostatic hypertrophy; and an added diagnosis of cardiac failure was made.

The patient received 18 grains of digitalis over a period of three days. In the meantime, he developed intermittent pain over the precordial area. A friction rub, which lasted

for one day, was heard in the cardiac apex. The temperature at that time was 100.4° F., the leucocytes numbered 9,450, and the sedimentation rate was 10 mm. in one hour. There was an onset of diarrhea. Suddenly on the sixth day after admission his pulse could not be palpated, he complained of gaseous distention, became comatose, and expired.

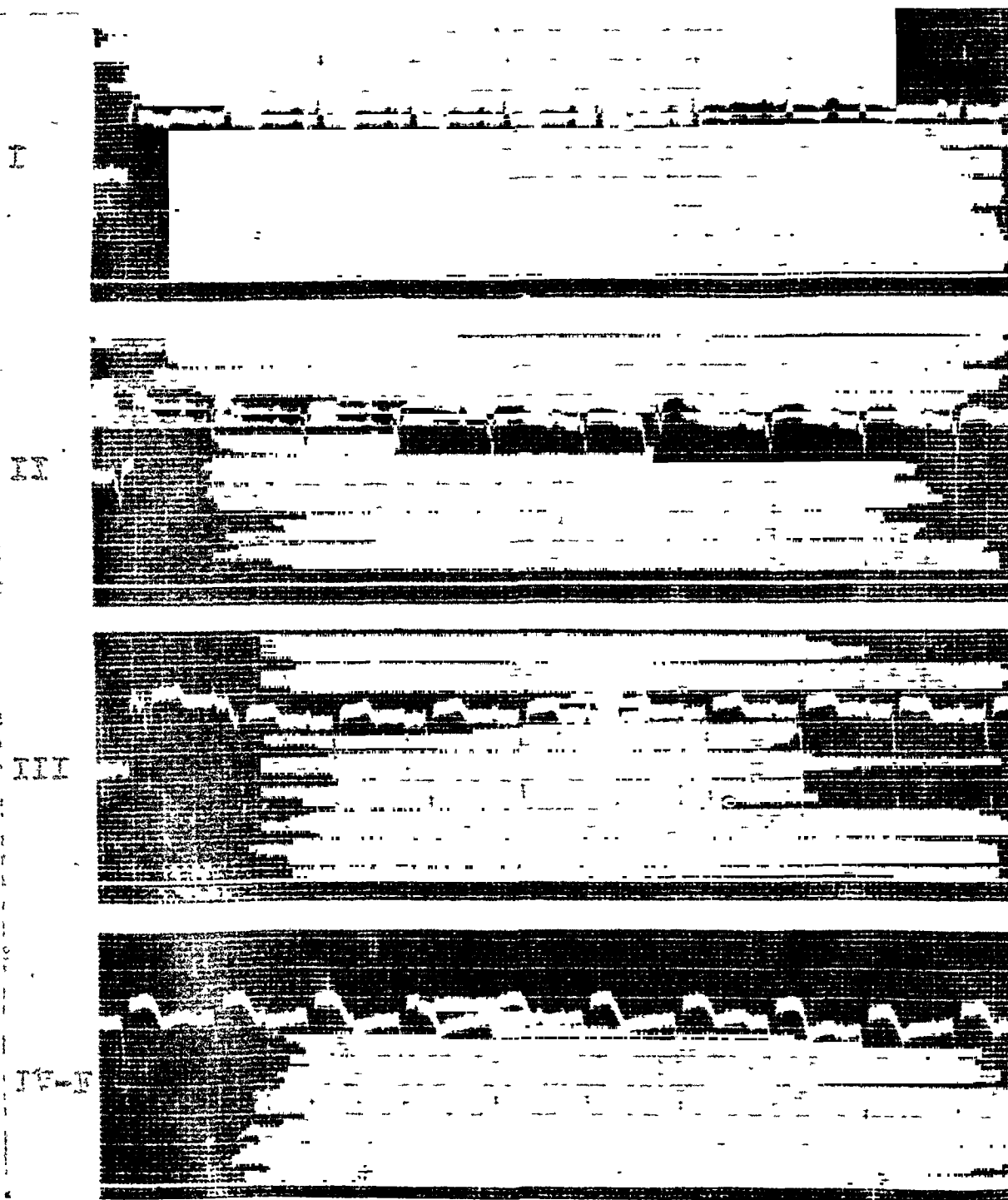


Fig. 3.—Electrocardiogram taken second day of last admission, showing diphasic T waves in Leads I, II, and IVF; slightly elevated S-T segments in Leads II, III, and IVF; and deep S waves in Leads II, III, and IVF, with absence of R wave in Lead IVF.

*Autopsy.**—External appearance: The body was that of a well-developed, well-nourished, white man. There was no rigor mortis, jaundice, or edema. There was cyanosis, Grade 2, of the nails and lips and mild hypostasis. On the anterior chest wall there were several petechiae.

Thoracic cavity: There was no fluid in the thoracic cavity. Adhesions were absent on the left side but present on the right side posteriorly and laterally. The pericardial sac was markedly dilated and filled with blood and blood clots. Crepitus was decreased at both pulmonary bases. The color was a darker red at the bases. Anthracosis, Grade 2, was present.

*Autopsy was performed by Dr. Don Beaver, Director of Pathology, Alexander Blain Hospital, and Woman's Hospital, Detroit, Michigan.

The heart weighed 740 grams. The epicardium was slightly granular and slightly hemorrhagic. At the apex there were dense, fibrous adhesions present which obliterated the pericardial sac. The right auricle was dilated Grade 2. The foramen ovale was closed. The tricuspid valve was normal, the right ventricle was slightly dilated. The muscle was about 1 cm. in greatest thickness. The pulmonary valve was normal. The left auricle was dilated, Grade 2, and the mitral valve was normal. The left ventricle was dilated at the apex into a sac measuring about 8 cm. in diameter. Over the endocardium of the sac there were firm, adherent, blood clots. These were detached with difficulty. The myocardium of the apex, septum, and sac had undergone fibrosis. At one point on the sac the muscle was very thin and soft, and at that point there was a stellate perforation, measuring 1 cm. in length. The right coronary artery was normal at the orifice, but there was considerable calcification of the aorta surrounding the orifice. The vessel itself was large, dilated, and about 3 cm. from its origin there was a patch of arteriosclerosis about $1\frac{1}{2}$ cm. in length;

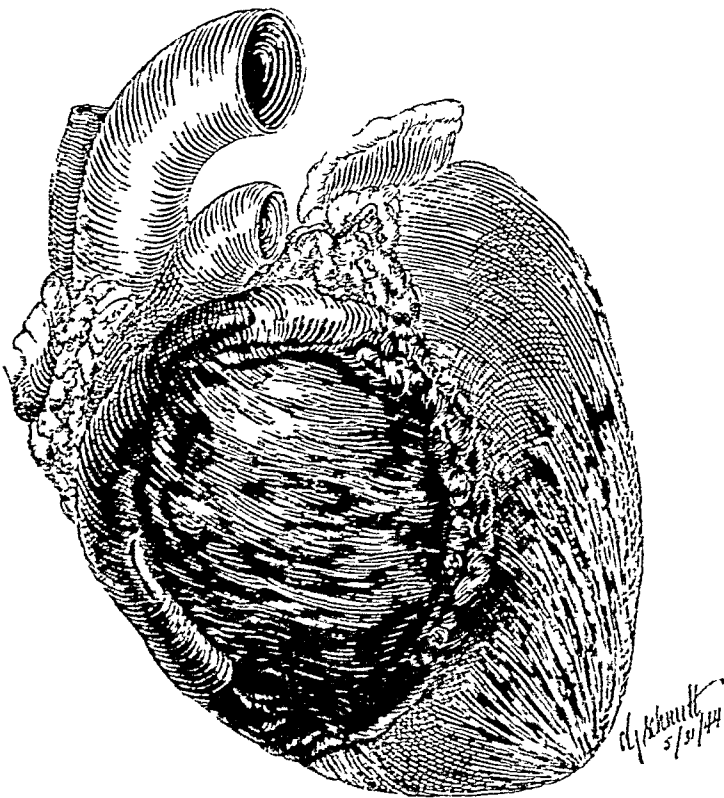


Fig. 1.—Drawing of external surface of heart revealing the saccular aneurysm of the left ventricle, involving the anterior surface. Note the slitlike perforation of the aneurysm at the midportion of the lower margin. The fibrous thickening of the epicardium surrounding the aneurysmal sac is also noteworthy.

however, there was no occlusion at this point. The left coronary artery was normal at the orifice. The circumflex branch was dilated and free from occlusions. The anterior descending branch showed considerable arteriosclerosis and calcification about $1\frac{1}{2}$ cm. from the origin of the vessel. At that point the lumen was occluded by arteriosclerotic changes. No thrombosis was found. The ascending aorta was dilated, Grade 2. The aortic valve cusps were partially calcified, and the valve ring was dilated. The aorta revealed sclerosis, Grade 1, except at the valve ring and around the coronary orifices where it was Grade 2 to 3.

Peritoneal cavity: The spleen weighed 100 grams. There was an old healed infarct about 7 cm. in diameter on the lateral surface. The trabeculae and follicles were distinct. The capsule was smooth.

The left kidney weighed 125 grams. The capsule stripped with ease, revealing a smooth surface which had a small, white area 1 cm. in diameter on the lateral edge. The ureter, pelvis, and medulla were normal. The cortex was normal, except for the white area. The right kidney weighed 125 grams. The capsule stripped with ease, revealing a smooth surface which had a red area $1\frac{1}{2}$ cm. in diameter and a white area 1 cm. in diameter. Except for these two areas, the cortex and medulla were normal. The pelvis and ureter were normal. No further examining was done.

Microscopic findings: Examination of the heart revealed that the myocardium was atrophic and replaced by scar tissue. At the endocardial margin there was an organizing thrombus. The epicardium was thickened and fibrous.

Anatomic and microscopic diagnoses: (1) Coronary arteriosclerosis with occlusion (anterior descending branch); (2) Healed infarct of apex of left ventricle, with scarring and formation of aneurysm; (3) Recent perforation of the cardiac aneurysm with hemo-pericardium; (4) Old healed infarct of spleen and kidneys plus recent infarct of right kidney; (5) Old healed pericarditis; and (6) Arteriosclerosis of aorta and aortic valve ring.

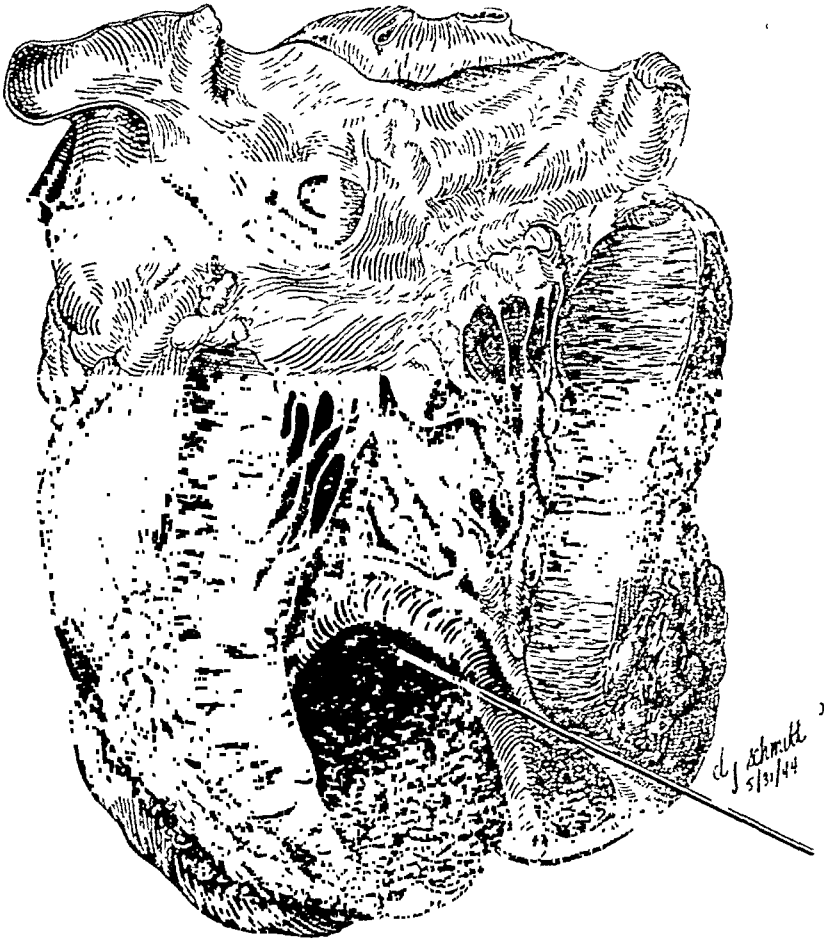


Fig. 5.—Drawing of heart with the left auricle and ventricle opened, disclosing the mitral valve leaflets. The chordae tendineae are attached to anterior and posterior papillary muscles. Aneurysmal dilatation is observed in apical portion of the left ventricle, extending toward the septum and toward the anterior surface below. Note the fibrous thickening of the epicardium over the left ventricle and the aneurysm. Note also the extremely thin muscle which forms the wall of the aneurysmal sac.

DISCUSSION AND SUMMARY

A case of ruptured cardiac aneurysm, verified by autopsy, is reported. The classical signs of aneurysm of the heart are described. However, those which were feasible to look for were not present in this case, making it impossible to diagnose this condition in life. Rupture of cardiac aneurysm is very rare. The electrocardiogram in this case resembled very closely the pattern described by Nordenfelt¹⁵ as diagnostic of cardiac aneurysm of the anterior wall of the left ventricle. When sudden death occurs during the course of coronary heart disease, especially when there has been a history of previous myocardial infarction, rupture of a cardiac aneurysm should be considered. It would seem that adequate rest following myocardial infarction did not prevent the formation of a cardiac aneurysm in this patient.

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THE ELECTROCARDIOGRAM IN HYPERTENSION

I. ITS DESCRIPTION

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THE electrocardiogram is of value in the diagnosis and prognosis of hypertension and hypertensive heart disease and may be of value in the determination of suitable cases for surgical treatment of hypertension by splanchnic resection.¹ Changes occurring in the electrocardiogram in hypertension have been described many times;²⁻¹⁴ however, very few correlations have been made, and changes in the T waves in Leads II and III have rarely been mentioned and have not been stressed. Also there has been but little experience with the multiple precordial leads in hypertension. The surgical treatment of hypertension has afforded us an opportunity to study changes in the electrocardiogram and to make numerous correlations between these and other changes concomitant with hypertension, including pathologic changes in the kidneys.

A. THE LIMB LEADS

Two hundred nine consecutive hypertensive patients, upon whom lumbo-dorsal sympathectomies were performed by R. H. Smithwick at the Massachusetts General Hospital, were selected for study. One hundred fifty electrocardiograms taken on 132 of the patients were suitable for analysis, that is, each record was taken with the patient in recumbency, and there were no com-

plicating factors such as digitalis effect or congenital or rheumatic heart disease; the additional eighteen records were follow-up electrocardiograms on several of the 132 patients at later dates. The ages of the 132 patients varied from 22 to 58 years with an average age of 40 years. The known duration of hypertension ranged from two months to twenty-four years. Eye grounds and renal biopsies varied from normal to Grade 4. Hearts were normal to large by teleroentgenogram. Electrocardiograms were normal to very abnormal.

One patient was said to have had an acute myocardial infarction about one month before operation, and another patient was said previously to have had a posterior myocardial infarction, but their electrocardiograms showed no evidence of such complications.

We believe that this material represents a good cross section of what one may expect to find in hypertension.

CHANGES IN THE LIMB LEAD ELECTROCARDIOGRAM ASSOCIATED WITH HYPERTENSION

Gross analysis of the 150 electrocardiograms (Table I) revealed that 34.7 per cent were within normal limits, 27.3 per cent had abnormal T waves only, 16 per cent had left axis deviation only, and 22 per cent had left axis deviation and T wave abnormalities. The T wave in Lead I was referred to in this and subsequent tables unless otherwise specified because the most consistent and most marked changes usually occurred in the T wave in that lead. Many times the T waves or axis deviation were within the normal (Fig. 1) but sometimes they were very close to the borderline between normal and abnormal. Occasionally their contours were such that slight adverse alterations in the T wave or electrical axis would have caused them to be abnormal.

Early changes in the electrocardiogram consisted of depression of the RS-T junction, the RS-T segment, and the T wave in Lead I (Fig. 3). In only six of the 150 electrocardiograms did the RS-T junction appear above the isoelectric line. Two of these were not included in Table II because the level of the RS-T junction in Lead III could not be determined accurately in these cases or in the remaining three of the total group of 150. It appeared at the isoelectric line thirty-five times and below that level 106 times. By the time the T wave became zero to 1 mm. in height, the RS-T junction was found above the isoelectric line in only one instance (4 per cent) or below it in nineteen (76 per cent). By the time the T wave became diphasic or inverted, the RS-T junction was found below the isoelectric line in all but one instance when it was at that level (Table III). The most striking changes occurred in the last portion of the RS-T segment and in the first portion of the T wave in Lead I so that the T wave first became diphasic (the minus, plus type) and later inverted. While the T wave was still upright, the RS-T segment was concave upward, but by the time the T wave became completely inverted, the RS-T segment was convex upward; that is, the convexity of the RS-T segment was opposite in direction to that of the T wave.

Concomitant with changes in Lead I were changes in the electrical axis, increase in length of the QT interval, and alterations in the RS-T junctions, the RS-T segments, and the T waves in Leads II and III. When measurable, shifts in the RS-T junctions and segments were found to have occurred in the same direction as those of the T waves. Many times, however, the RS-T junction and segment changes were insignificant and difficult to measure.

TABLE I. GROSS ANALYSIS OF THE LIMB LEADS OF THE ELECTROCARDIOGRAM IN HYPERTENSION

NUMBER OF ECG'S	NORMAL	T CHANGES* ONLY	L. A. D.† ONLY	L. A. D. AND T CHANGES	TOTAL ABNORMAL ECG'S
150	52 (34.7%)	41 (27.3%)	24 (16.0%)	33 (22.0%)	98 (65.3%)
Total number of T changes = 74 (49.3%)					
Total number of L.A.D. = 57 (38.0%)					

*T Changes = T less than 1 mm. in Lead I.

†L.A.D. = left axis deviation of 0° or greater (Einthoven's triangle).

Apparently the most common changes in Lead III were elevations of the RS-T junction, the RS-T segment, and the T wave (Figs. 5 and 6). By the time the RS-T junction in Lead I was found below the isoelectric line, the RS-T junction in Lead III was found above the isoelectric line in 41.5 per cent, at that level in 37.7 per cent, and below it in 20.8 per cent (Table II). It was impossible to be certain, however, that the RS-T junction had shifted up or down just because the junction was found to be above or below the isoelectric line. As the last part of the RS-T segment and the first part of the T wave in Lead I became depressed, the last part of the RS-T segment and the first part of the T wave in Lead III frequently became elevated. These alterations often produced "coronary" types of RS-T segments in Lead III (late inversion of the T waves with the RS-T segments at or above the isoelectric line) in electrocardiograms of patients in whom the T waves in Lead III were normally inverted. Not uncommonly, the T wave in Lead III became depressed so that a normally inverted T wave became more inverted. Changes in the T wave in Lead II almost always occurred in the same direction as those in Lead I since changes in Lead I almost always predominated over those in Lead III and Lead II is the algebraic sum of Leads I and III. By the same token, changes in Lead I predominated over those in Lead II in cases in which the T wave was depressed in Lead I and elevated in Lead III. They predominated in Lead II when the T wave was depressed in Lead III, as well as in Lead I.

Concerning inverted T waves per se, the T wave in Lead I was inverted fifty-one times; this abnormality appeared alone twenty-four times, with an inverted T wave in Lead II twenty times, and with inverted T waves in Leads II and III seven times. An inverted T wave in Lead III occurred in fifty-seven cases; alone thirty-six times, with an inverted T wave in Lead II fourteen times, and with inverted T waves in both Leads I and II seven times, as noted previously. *None of the inverted T waves in Lead I alone was associated with abnormal Q waves in Lead I.* Two of the electrocardiograms with inverted T waves in Leads I and II had abnormally large Q waves in Lead III but not in Lead I or Lead II. Neither of these two patients had angina pectoris. Of the seven electrocardiograms with inverted T waves in Leads I, II, and III, none had abnormal Q waves. Four had coronary type T waves in Lead III—late inversion of the T wave with the RS-T junction at or above the isoelectric line. The RS-T junction in Lead I was depressed in each instance. None of these seven patients had angina pectoris. Postoperative follow-up electrocardiograms of five of the seven patients showed improvement in two tracings, no change in two, and adverse change in one. Of the fourteen electrocardiograms with inverted T waves in Leads II and III, only one had possibly abnormal Q waves. The T waves in Lead I were normal in five cases and low (less than 1 mm.) but upright in the other nine. The RS-T junctions in Lead I were depressed in all. Of three patients whose postoperative follow-up electrocardiograms had

returned to normal, all had normally inverted T waves in Lead III. None of these fourteen patients had angina pectoris; however, in two the question of a recent posterior myocardial infarct was raised. The most frequent form of RS-T segment was the one in which the T wave was upright and the RS-T segment was below the isoelectric line and was concave. This form represents 87.3 per cent of the 150 Lead I's, 86.0 per cent of the Lead II's, and 85.3 per cent of the Lead III's. Lead III was the only lead to show a coronary type RS-T segment. Sixteen other forms of the RS-T segment occurred, but their frequency was insufficient to warrant emphasis.

Concerning abnormal Q waves per se, Q waves in Lead I were considered to be abnormally large on two occasions. In one, the Q wave was only 2 mm. in amplitude, but the maximal QRS deflection was only 10 millimeters. In the other, the Q wave was $2\frac{1}{2}$ mm., and the greatest QRS deflection was 13 millimeters. The T waves in Lead I were normal in both. Neither patient had angina pectoris. The Q wave in Lead III was large on fourteen occasions (eleven patients). In three electrocardiograms it was in the form of QS. Small Q waves in Lead II (less than 2 mm.) were present in five of these fourteen cases. The T waves were inverted in Leads II and III in two of the cases. There were no Q waves in Lead II alone.

The QT interval was prolonged above the predicted average normal¹⁵ in almost all of the otherwise abnormal electrocardiograms and in many of the otherwise normal tracings (Table IV).

Changes in the electrical axis occurred simultaneously with those in the T waves in Lead I. Usually the changes were in accord, that is, when the T wave in Lead I became more depressed, the axis shifted more to the left and vice versa. There were many exceptions, however, and the relative change in each varied considerably in different cases.

Changes in the P-R interval or the duration of the QRS complexes may have occurred although these intervals were not prolonged above the range of normal in any record.

CORRELATIONS

In Table II the RS-T junctions in Lead I in 145 of the 150 electrocardiograms were correlated with the RS-T junctions in Lead III. In only four electrocardiograms were the RS-T junctions above the isoelectric line in Lead I. In 106 (73.1 per cent) the junctions were below the isoelectric line, and in 35 (24.1 per cent) they were at that level. From these data it appeared that the depression of the RS-T junction in Lead I was a relatively early and permanent change

TABLE II. CORRELATION OF RS-T JUNCTION IN LEAD I WITH RS-T JUNCTION IN LEAD III

NUMBER OF ECG'S			NUMBER OF ECG'S		
RS-T ₁	elevated	4	RS-T ₂	elevated	2 (50.0%)
				level	2 (50.0%)
				depressed	0 (0.0%)
RS-T ₁	level	35	RS-T ₂	elevated	4 (11.4%)
				level	17 (48.6%)
				depressed	14 (40.0%)
RS-T ₁	depressed	106	RS-T ₂	elevated	44 (41.5%)
				level	40 (37.7%)
				depressed	22 (20.8%)

TABLE III. CORRELATION OF T WAVE IN LEAD I WITH RS-T JUNCTION IN LEAD I

NUMBER OF ECG'S			
T ₁ 0 to 1 mm.	25	RS-T ₁	+ 1 (4.0%) 0 5 (20.0%) - 19 (76.0%)
T ₁ diphasic or inverted	49	RS-T ₁	+ 0 (0.0%) 0 1 (2.0%) - 48 (98.0%)

in the electrocardiogram in hypertension. Electrocardiograms with the RS-T junction above the isoelectric line in Lead I were so few that a statistical analysis of the associated levels of the RS-T junction in Lead III was of little value. When the junction was at the isoelectric line in Lead I, it appeared below that level in Lead III four times as frequently as it did above it. By the time the RS-T junction was below the isoelectric line in Lead I, the junction appeared above that level in Lead III twice as often as it did below it. From these data, it appeared that elevation of the RS-T junction was the most common change in Lead III.

In Table III the RS-T junction in Lead I was correlated with the height of the T wave in that lead. When the T wave measured in height from zero to 1 mm., the RS-T junction appeared above the isoelectric line only once (4 per cent). By the time the T waves became diphasic or inverted, all but one (98 per cent) of the RS-T segments appeared below the isoelectric line, and none appeared above it. These data substantiate the permanency of the RS-T junction depression and afford important information for the differential diagnosis between the electrocardiogram in hypertension and that in coronary disease.

The QT interval was correlated with other findings in the electrocardiogram in Table IV. Many times the end point of the QT interval was not clear-cut, but it was possible to obtain reasonably accurate measurements in 138 records. The measured QT interval was compared with the predicted normal interval and the range of normal. When the QT interval was at the predicted normal or below, 81.3 per cent of the electrocardiograms were normal otherwise, and when the QT interval was above the range of normal 72.6 per cent were abnormal otherwise.

Table IV may be broken down another way as follows: of the fifty-two normal electrocardiograms, 25 per cent had QT intervals at or below the predicted normal, 30.8 per cent above the predicted average normal but within the range of normal, and 44.2 per cent definitely above the normal range. Of the eighty-six electrocardiograms which were abnormal otherwise, only 3.5 per cent had QT intervals which were at or below the predicted normal while 25.6 per

TABLE IV. CORRELATION OF THE QT INTERVAL WITH OTHER CHANGES IN THE ELECTROCARDIOGRAM

THE QT INTERVAL	NUMBER OF ECG'S (138)	NORMAL (52)	T CHANGES ONLY	L.A.D. ONLY	T CHANGES AND L.A.D.	TOTAL ABNORMAL ECG'S (86)
1. Predicted normal or below*	16	13 (81.3%) (25.0%)	0 (0%)	1 (6.2%)	2 (12.5%)	3 (18.7%) (3.5%)
2. Above predicted normal but within normal range	38	16 (42.1%) (30.8%)	8 (21.0%)	5 (13.2%)	9 (23.7%)	23 (57.9%) (25.6%)
3. Above normal range	84	23 (27.4%) (44.2%)	25 (29.8%)	18 (21.4%)	18 (21.4%)	61 (72.6%) (70.9%)

*As determined by the prediction table of Ashman and Hull.¹⁵

cent had QT intervals above the predicted normal but below the upper limit of normal, and 70.9 per cent had QT intervals above the range of normal.

Electrocardiographic changes were correlated with eye-ground findings in Table V. Criteria for grading the eye grounds were as follows: normal, no abnormal findings in the retina; Grade 1, minimal caliber changes in the retinal arterioles; Grade 2, caliber changes with arteriovenous nicking; Grade 3, hemorrhages and exudates; Grade 4, changes as in Grade 3 plus papilledema. Eliminating one electrocardiogram in which the eye grounds were normal, there was a tendency for the electrocardiogram to become more abnormal as the eye grounds became worse.

TABLE V. CORRELATION OF ELECTROCARDIOGRAPHIC CHANGES WITH THE EYE-GROUND CLASSIFICATION

EYE GROUNDS	NUMBER OF		T CHANGES ONLY	L.A.D. ONLY	T CHANGES AND L.A.D.	TOTAL ABNORMAL ECG'S
	ECG'S	NORMAL				
Normal	1	0 (0%)	1 (100%)	0 (0%)	0 (0%)	1 (100%)
Grade 1	44	23 (52.3%)	7 (15.9%)	5 (11.3%)	9 (20.5%)	21 (47.7%)
Grade 2	29	12 (41.4%)	9 (31.0%)	3 (10.4%)	5 (17.2%)	17 (58.6%)
Grade 3	50	12 (24.0%)	15 (30.0%)	9 (18.0%)	14 (28.0%)	38 (76.0%)
Grade 4	26	5 (19.2%)	9 (34.6%)	7 (26.9%)	5 (19.2%)	21 (80.7%)

In Table VI changes in the electrocardiogram were correlated with pathologic findings in the renal biopsies. The biopsies were classified into five groups as follows: Grade 0, no abnormal findings seen; Grade 1, slight amount of vascular change (predominantly arteriolar intimal hyalinization and arterial endothelial hyperplasia); Grade 2, slightly more vascular change than in Grade 1, and an occasional hyalinized glomerulus; Grade 3, severe vascular disease in every vessel with predominant medial arteriolar hypertrophy and many hyalinized glomeruli; Grade 4, involvement of every vessel, scarring of many glomeruli and atrophy of surrounding tubules.¹⁶ There appeared to be no definite positive correlation between alterations in the electrocardiogram and pathologic changes in the kidney except that, in the group with Grade 4 kidneys, the incidence of abnormal tracings was distinctly greater than in the other groups.

Correlations with the heart size were made in Table VII. The heart size in each instance was based on the roentgenologist's opinion with the addition of

TABLE VI. CORRELATION OF ELECTROCARDIOGRAPHIC CHANGES WITH RENAL BIOPSIES

RENAL GRADE	NUMBER OF		T CHANGES ONLY	L.A.D. ONLY	T CHANGES AND L.A.D.	TOTAL ABNORMAL ECG'S
	ECG'S	NORMAL				
0	8	3 (37.5%)	2 (25.0%)	1 (12.5%)	2 (25.0%)	5 (62.5%)
1	20	7 (35.0%)	4 (20.0%)	3 (15.0%)	6 (30.0%)	13 (65.0%)
2	29	9 (31.0%)	9 (31.0%)	5 (17.2%)	6 (20.7%)	20 (68.9%)
3	36	14 (38.9%)	10 (27.8%)	3 (8.3%)	9 (25.0%)	22 (61.1%)
4	20	3 (15.0%)	5 (25.0%)	4 (20.0%)	8 (40.0%)	17 (85.0%)

TABLE VII. CORRELATION OF ELECTROCARDIOGRAPHIC CHANGES WITH HEART SIZE BY TELEROENTGENOGRAM

HEART SIZE	NUM- BER OF		T CHANGES ONLY	L.A.D. ONLY	T CHANGES AND L.A.D.	TOTAL ABNORMAL ECG'S
	ECG'S	NORMAL				
Normal	47	18 (38.3%)	14 (29.8%)	7 (14.9%)	8 (17.0%)	29 (61.9%)
Rounded apex (other- wise normal)	32	13 (40.6%)	6 (18.75%)	7 (21.9%)	6 (18.75%)	19 (59.4%)
Definitely enlarged	58	12 (20.7%)	18 (31.0%)	10 (17.3%)	18 (31.0%)	46 (79.3%)

measurements. There were a few more abnormal electrocardiograms in the group with enlarged hearts than in the group with normal hearts but no striking correlation was found. The T changes noted in the table relate to Lead I, as already stated.

Inverted and diphasic T waves in Lead II were also correlated with the heart size, and 39.4 per cent of the patients with abnormal T waves in Lead II were found to have hearts of normal size.

The electrocardiographic changes were correlated with the symptoms of chest pain and dyspnea in Table VIII. In the group in which the patients complained of dyspnea only, the number of abnormal electrocardiograms was not significantly greater than in the group without dyspnea. This was not true of the group with chest pain—by the time patients complained of chest pain, the electrocardiogram was abnormal in each instance. Abnormal T waves appeared in Lead I or II in 91.7 per cent of the cases. It so happened that none of the patients complaining of chest pain had abnormal Q waves or diphasic or inverted T waves in Leads I, II, and III, or in Leads II and III.

TABLE VIII. ELECTROCARDIOGRAPHIC CHANGES CORRELATED WITH CHEST PAIN AND DYSPNEA

SYMP-TOMS	NUM-BER OF ECG'S	NORMAL	T CHANGES ONLY	L.A.D. ONLY	T CHANGES AND L.A.D.	TOTAL ABNORMAL ECG'S
Dyspnea	50	16 (32.0%)	14 (28.0%)	8 (16.0%)	12 (24.0%)	34 (68.0%)
Pain	11	0 (0%)	6 (54.6%)	1 (9.0%)	4 (36.4%)	11 (100%)
Dyspnea and pain	1	0 (0%)	0 (0%)	0 (0%)	1 (100%)	1 (100%)
No dyspnea or pain	87	36 (41.4%)	21 (24.1%)	15 (17.3%)	15 (17.3%)	51 (58.6%)

In Table IX, electrocardiographic changes were correlated with the known duration of hypertension, and there appeared to be no definite relationship.

TABLE IX. CORRELATION OF ELECTROCARDIOGRAPHIC CHANGES WITH THE KNOWN DURATION OF HYPERTENSION

YEARS DURATION	NUM-BER OF ECG'S	NORMAL	T CHANGES ONLY	L.A.D. ONLY	T CHANGES AND L.A.D.	TOTAL ABNORMAL ECG'S
1	36	10 (27.8%)	12 (33.3%)	4 (11.1%)	10 (27.8%)	26 (72.2%)
2	19	7 (36.8%)	6 (31.6%)	3 (15.8%)	3 (15.8%)	12 (63.2%)
3	14	5 (35.7%)	2 (14.3%)	3 (21.4%)	4 (28.6%)	9 (64.3%)
4	16	7 (43.8%)	2 (12.5%)	5 (31.2%)	2 (12.5%)	9 (56.2%)
5	28	9 (32.1%)	11 (39.3%)	3 (10.7%)	5 (17.9%)	19 (67.9%)
10	23	11 (47.8%)	5 (21.7%)	4 (17.4%)	3 (13.1%)	12 (52.2%)
15	4	3 (75.0%)	0 (0%)	0 (0%)	1 (25.0%)	1 (25.0%)
20	7	0 (0%)	3 (42.8%)	2 (28.6%)	2 (28.6%)	7 (100%)
25	1	0 (0%)	0 (0%)	0 (0%)	1 (100%)	1 (100%)

In Table X, electrocardiographic changes were correlated with the diastolic blood pressure on admission and no definite positive relationship was observed.

TABLE X. CORRELATION OF ELECTROCARDIOGRAPHIC CHANGES WITH THE DIASTOLIC BLOOD PRESSURE ON ADMISSION

DIASTOLIC PRESSURE	NUM-BER OF ECG'S	NORMAL	T CHANGES ONLY	L.A.D. ONLY	T CHANGES AND L.A.D.	TOTAL ABNORMAL ECG'S
90 or below	3	2 (66.7%)	1 (33.3%)	0 (0%)	0 (0%)	1 (33.3%)
91 to 120	53	19 (35.8%)	11 (20.8%)	10 (18.9%)	13 (24.5%)	34 (64.2%)
121 to 140	61	19 (31.1%)	16 (26.2%)	10 (16.4%)	16 (26.2%)	42 (68.8%)
Over 140	31	12 (38.7%)	12 (38.7%)	4 (12.9%)	3 (9.7%)	19 (61.3%)

In Table XI, electrocardiographic changes were correlated with the body build. This table is of interest in that nine (60 per cent) of the fifteen thin patients had T-wave changes without abnormal axis deviation, one (6.7 per cent) had T-wave changes and left axis deviation, five (33.3 per cent) had normal electrocardiograms, and none had left axis deviation without T-wave changes. In the short and fat or stocky groups, only five (19.2 per cent) had T-wave changes alone while nine (34.6 per cent) had axis and T-wave changes and five (19.2 per cent) had left axis deviation alone. Some of the patients who were described as stocky or short and fat were basically of thin build—the midclavicular line of one patient labelled as short and stocky was only 6.5 centimeters from the midsternum. This partially explains why some of these patients had T-wave changes without axis change.

TABLE XI. CORRELATION OF ELECTROCARDIOGRAPHIC CHANGES WITH THE BODY BUILD

BODY BUILD	NUMBER OF ECG'S	NORMAL	T CHANGES ONLY	L.A.D. ONLY	T CHANGES AND L.A.D.	TOTAL ABNORMAL ECG'S
Thin	15	5 (33.3%)	9 (60.0%)	0 (%)	1 (6.7%)	10 (66.7%)
Average	109	40 (36.7%)	27 (24.8%)	19 (17.4%)	23 (21.1%)	69 (63.3%)
Short and fat or stocky	26	7 (26.9%)	5 (19.2%)	5 (19.2%)	9 (34.6%)	19 (73.1%)

DISCUSSION

It is unlikely though remotely possible that the earliest change in the electrocardiogram in hypertension is an elevation of the RS-T segment in Lead I, as described by Robb and Robb.¹⁴ If this occurred in our series it must have been early and transient since in only six of the 150 electrocardiograms were the RS-T junctions found above the isoelectric line. The depression of the RS-T segment in Lead III in certain cases of hypertension could not with certainty be explained by strain on various muscle bundles as described by Robb and Robb; however, some such strain is probably the cause. Those workers found a depression of the RS-T segments in all three leads following a sudden rise in the pressure in the right ventricle in experimental animals, and it is possible that an acute rise in the pressure in the left ventricle may also produce similar changes. All of our patients with depressed RS-T segments in all leads had diastolic blood pressures between 130 and 160 mm. Hg except one, and this patient had a diastolic pressure of 115 mm. of mercury.

Lengthening of the QT interval has been previously described as an early manifestation of hypertension¹⁵; it may well be associated with enlargement—a stretching and hypertrophy of the muscle fibers.

As stated before, electrocardiographic alterations in hypertension have been mentioned many times.²⁻¹⁴ Inversion of the T wave in Lead I and axis changes have been usually stressed. Rykert and Hepburn¹⁰ presented an early and important paper calling attention to the fact that inversion of the T wave in Lead I can result from hypertension alone without coronary heart disease per se. Only rarely have changes in the T waves in Leads II and III, or I, II, and III been mentioned, however, and never have they been stressed. Depression of the RS-T segment in Lead III has not been described. Willius reported 130 cases in which there was negativity of the T waves due to any cause and upon which autopsies were performed. Fifty-four of the patients had hypertensive heart disease. Electrocardiograms of thirteen (25 per cent) of these patients showed inverted T waves in Leads I, II, and III, and five (9.6 per cent) showed inverted T waves in Leads II and III. Ninety-two per cent of all patients

with negative T waves in Leads I, II, and III from any cause showed 1 to 4 plus sclerosis of the coronary vessels and 69 per cent of those with inverted T waves in Leads II and III showed coronary sclerosis. Barnes and Whitten,⁷ reporting on 117 patients with significant T wave changes, upon whom necropsies were performed, mentioned that 7 per cent showed inversion of the T waves in Leads II and III, and 9.4 per cent showed inversion in Leads I, II, and III. They stated that when inversion of T waves occurred in Leads II and III, one should suspect some condition causing an overload on the right ventricle or a posterior myocardial infarction. Kaplan and Katz¹³ stated that ten of fifty-two records with axis deviation and T-wave changes differed from the classical pattern in that the T wave in Lead III was inverted. Some of the books on electrocardiography,^{15, 17-19} have stressed the changes in the T wave in Lead I but not those in II and III. Several of the electrocardiograms in hypertension presented by Katz¹⁹ had abnormal T waves in the three standard leads, and one showed striking depression of the RS-T segments and T waves in the three leads.

It is not difficult to visualize why inversion of the T waves occurs in Leads II and III or later in Leads I, II, and III in patients who have normally inverted T waves in Lead III when marked changes occur in Lead I and little or no changes occur in Lead III or when there is depression of the RS-T segments in Lead III, as well as in Leads I and II. The facts that they may occur in the electrocardiograms of young people who are not suspected of having coronary disease and do not have angina pectoris, that they are not associated with abnormal Q waves, and that the electrocardiogram may return to normal with a normally inverted T wave in Lead III following sympathectomy lend support to the theory that changes in the T waves in Leads II and III alone, or in combination with changes in the T wave in Lead I,²⁰ may be caused by hypertension, per se, without coronary disease or superimposed right ventricular strain; heart position related to body build is undoubtedly an important factor in these cases as it is in the cases to be mentioned.

Superimposed right ventricular strain has held an important place in the explanation of T-wave changes without left axis deviation. A few investigators, especially Wilson et al.,^{5, 21} have emphasized the role that position of the heart within the thorax plays in this picture. Special emphasis on alterations of the T wave in Lead II with changes in the position of the body have been reported several times.^{22, 23} Knowing that body build greatly influenced the position of the heart within the thorax we correlated electrocardiographic changes with the body build. Since T-wave and axis changes occur in the electrocardiogram in hypertension, it is logical to assume that a vertically placed heart or one so rotated that the electrical potential of the left ventricle is transmitted to the left leg would develop abnormal T waves before it would left axis deviation and that in a transversely placed heart or one so rotated that the potential of the left ventricle is transmitted to the left arm, left axis deviation without abnormal T waves is likely to occur. These assumptions were quite well supported by our data. Of fifteen patients, who were of thin build, nine (60 per cent) showed T changes only, one showed abnormal T waves and left axis deviation, and none showed left axis deviation without abnormal T waves. Of twenty-six patients, who were short and fat, or stocky, five (19.2 per cent) had left axis deviation without abnormal T waves, nine (34.6 per cent) had left axis deviation and abnormal T waves, and five (19.2 per cent) had abnormal T waves without left axis deviation. T-wave abnormalities without left axis deviation may be accounted for in several ways: (1) a tendency for T waves to become markedly altered before significant axis changes appear in certain

individuals when there are sudden rises in intraventricular pressure; (2) rotation of the heart in some stocky persons so that the electrical potential of the left ventricle is transmitted to the left leg; and (3) misinterpretation of body build. Some patients who are short and fat and appear to be stocky are fundamentally of thin build as to thorax. The midclavicular line of one of our patients who was placed in this group was only 6.5 cm. from the midsternum.

We believe that T-wave changes in the absence of coronary heart disease are dependent mainly upon four variables, at least two of which interfere with the normal function of the heart, including conduction: (1) dilatation, (2) hypertrophy or increased muscle mass without compensatory increase in the vascular bed, (3) increased work with subsequent rise in myocardial metabolism, and (4) rotation of the heart on its longitudinal or transverse axis. Slight to moderate changes in heart rate affect the T waves only a little but marked changes in rate, such as that which occurs in paroxysmal tachycardia, may alter them considerably, causing their depression during faster rates.

That T-wave changes are not necessarily due to coronary heart disease is partially confirmed by the fact that when the heart is relieved of "strain" by a decrease in the blood pressure, such as frequently happens following sympathectomy, the T waves may return to normal. The "strain" on the heart is relieved so that myocardial metabolism is lowered and dilatation is lessened. Probably the position of the heart is also altered to some extent.

Other investigators have commented on the lack of definite positive correlation between the heart size and the electrocardiographic changes.^{7, 8, 12, 13} Our data showed that the incidence of abnormal electrocardiograms was slightly greater in the group with enlarged hearts than in the one with hearts of normal size. Schnur²⁵ found the heart to be enlarged in every case in his series in which the T wave was inverted in Lead II, but it was not uncommon in our series to find inverted T waves in Lead II associated with hearts of normal size by teleroentgenogram (39.4 per cent of the patients with inverted T waves in Lead II had hearts of normal size). It is, however, difficult or impossible to recognize slight, or indeed even moderate, cardiac enlargement in many cases by roentgen-ray examination, particularly when there is very little dilatation; it is quite possible that in some cases, at least, the electrocardiogram is a more sensitive index of enlargement of the heart than is the roentgenogram.

A trend toward a positive correlation between the electrocardiographic changes and the degree of retinal changes was noted by Roesler and co-workers.¹² In our series, the electrocardiogram tended to become more abnormal as the eye grounds became worse.

The diastolic pressure on admission to the hospital is notoriously an inaccurate measurement of the individual's usual blood pressure, since it depends so much on many variables, such as the general condition of the patient, the attitude and acuity of hearing of the examiner, and the position of the patient. However, it does give some information as to what height the blood pressure may rise, hence it was correlated with electrocardiographic changes in our cases. No definite positive correlations could be found between the two.

Almost the same statement is true with respect to the correlation between the known duration of the hypertension and electrocardiographic findings. It is a well-known fact that the stated duration of hypertension is a poor estimate of the actual duration and gives no information as to the strain on the heart.

Dyspnea and chest pain may be misleading since they can be due to conditions other than myocardial and coronary insufficiency; however, there was a striking correlation between chest pain and changes in the electrocardiogram. Of the twelve patients who complained of chest pain, all but one had abnormal T waves in Lead I. Peculiarly, there were no abnormal Q waves, conduction defects, or abnormal T waves in Leads II and III among these cases.

SUMMARY AND CONCLUSIONS (A. THE LIMB LEADS)

1. Two hundred nine consecutive patients, upon whom dorsolumbar sympathectomies were performed by R. H. Smithwick at the Massachusetts General Hospital, were selected for study. One hundred fifty electrocardiograms on 132 patients were suitable for analysis. The patients' ages varied from 22 to 58 years, with an average age of 40 years. The known duration of hypertension ranged from two months to twenty-four years. Eye grounds and renal biopsies varied from normal to Grade 4. Hearts were normal to large by teleroentgenogram. The diastolic blood pressure on admission varied from 88 to 180 mm. of mercury.

2. Correlations were made between electrocardiographic changes in the limb leads and (a) the known duration of hypertension, (b) the height of the diastolic pressure on admission, (c) the heart size by teleroentgenogram, (d) symptoms (chest pain and dyspnea), (e) eye-ground findings, and (f) pathological changes in the kidneys found in biopsy material.

3. Gross analysis of the electrocardiograms revealed that 34.7 per cent were within the range of normal, 27.3 per cent showed abnormal T waves only (less than 1 mm. in height in Lead I), 16 per cent showed left axis deviation only (zero or minus according to Einthoven's triangle), and 22 per cent showed left axis deviation plus abnormal T waves.

4. Early electrocardiographic changes consisted of depression of the RS-T junction and segment in Lead I, lowering of the T wave in Lead I, and lengthening of the QT interval.

5. Axis changes occurred simultaneously with T-wave changes in Lead I but were variable. Sometimes considerable axis change occurred while only slight T-wave alterations appeared and vice versa.

6. Concomitant with changes in the T-wave in Lead I, the most frequent change in Lead III was an elevation of the RS-T segment.

7. Many times the relative changes in Lead III were slight and sometimes the RS-T segment in Lead III, as well as that in Lead I, was depressed.

8. In the electrocardiograms in which the T waves were normally inverted in Lead III, inversion of the T waves first appeared in Leads II and III and later in Leads I, II, and III when there was considerable change in Lead I with only slight change in Lead III or when the RS-T segment was depressed in Lead III as well as Lead I.

9. In the electrocardiograms in which the T waves in Lead III were normally inverted, coronary type T waves appeared in the cases in which the last portion of the RS-T segment and the first portion of the T wave became elevated.

10. Changes in the RS-T segments in Leads II and III are important since they have not been stressed and they frequently have been misinterpreted as changes due to coronary disease.

11. Electrocardiograms tended to become more abnormal as eye-ground changes became worse.

12. There was no definite positive correlation between changes in the electrocardiogram and those in the renal biopsy material; however, the incidence of abnormal electrocardiograms was distinctly greater in the group with Grade 4 renal biopsies than in the other groups.

13. The incidence of abnormal electrocardiograms was only slightly greater in the group with obviously enlarged hearts by roentgen-ray examination than in the one with "normal" sized hearts.

14. The T wave in Lead II may be inverted in hearts of "normal" size.

15. By the time patients complained of pain in the chest, the T waves in Lead I had become abnormal in 91.7 per cent.

16. No positive correlation appeared between dyspnea and electrocardiographic changes.

17. No definite positive correlation was found between electrocardiographic alterations and the known duration of hypertension or the diastolic blood pressure on admission to the hospital.

B. THE PRECORDIAL LEADS

Smithwick's preoperative studies have provided us with excellent material for the analysis of the precordial leads in hypertension. We have been taking precordial Leads CF_2 , CF_4 , and CF_5 routinely, according to the standards established by the American Heart Association, on all hypertensive patients who are seen for consideration of lumbodorsal sympathectomy. The CF leads are those in which the precordial electrode is paired with an indifferent electrode attached to the left leg, and the positions on the chest are as follows: in taking Lead CF_2 , the precordial electrode is placed in the fourth intercostal space just to the left of the sternum; in taking Lead CF_4 it is placed in the fifth intercostal space at the midclavicular line; and in taking Lead CF_5 it is placed in the fifth intercostal space at the anterior axillary line (or in the sixth space if the cardiac apex is located in that space). These three precordial leads have been selected for routine use at the Massachusetts General Hospital because they have been found clinically useful and practicable more often than other combinations.

The present study includes one hundred such electrocardiograms of one hundred cases, for the most part taken consecutively except for the omission of those cases in which digitalis had been given. The ages of the patients varied from 17 to 66 years, averaging 42.4 years, with the distribution of age groups as follows: 45 per cent between 40 and 50 years; 22 per cent between 30 and 40 years; 19 per cent between 50 and 60 years; 9 per cent between 20 and 30 years; 3 per cent between 60 and 70 years; and 2 per cent under 20 years. This group is probably quite representative of hypertensive patients, but it must be remembered that they are somewhat selected patients since a great deal of work was often done before admission to determine whether they were suitable candidates for operation.

The duration of hypertension was known with reasonable certainty in only seventy-three of the one hundred cases. In these it had been present for from four months to twenty years with an average duration of 5.6 years. The systolic and diastolic pressures of the individual patients varied so widely that an accurate average was difficult to obtain. In some cases only one or two admission readings were available; in other cases an average of several readings, some of which were taken after the patient had been at rest in bed for several days, often failed to indicate the severity of the hypertension. However, taking the best average reading obtainable for each patient, we found the diastolic blood pressure 100 mm. or more in ninety-seven cases and

TABLE XII. AMPLITUDE AND DIRECTIONS OF ELECTROCARDIOGRAPHIC COMPLEXES IN HYPERTENSION AS COMPARED WITH THE NORMAL

	R WAVE		S WAVE		T WAVE		DEVIATION OF S-T SEGMENT FROM P-R		MAXI- MAL R	MINI- MAL R	MAXI- MAL S	MINI- MAL S	MAXI- MAL T	MINI- MAL T
	DIRECTION OF DEFLECTION	AV. AMPLITUDE IN MM.	DIRECTION OF DEFLECTION	AV. AMPLITUDE IN MM.	DIRECTION OF DEFLECTION	AV. AMPLITUDE IN MM.	DIRECTION OF DEFLECTION	AV. DEVIATION IN MM.						
CF ₃														
10 Normal Adults (Deeds and Barnes)	+10	+6.4	-10	-23.7	+10	+6	+10	+1.9						
50 Normal Males (Deeds and Barnes)	+50	+8.4	-50	-25.4	+50	+7.1	+50	+1.9	16.8	1.1	35	7	+15.5	+3.1
50 Normal Females (Deeds and Barnes)	+50	+4.6	-50	-24.5	+49 0	+4.3	+49	+1.3	10.7	0.2	35	12	+10.1	+1.7
100 Normal Persons (Shanno)	+100	+4.7		-19--22	diphasic 1 +94 -6	1-4	level 1		13	1	31	9	+7	-2
Our 100 Hypertensive Patients	+100	+4.1	-100	-20.6	+98 -2	5.02	level 23	0.5-3.5	Not known	0-1	Not known	0-1	+11	0
IVF (OR CF ₁)														
10 Normal Adults (Deeds and Barnes)	+10	+7.5	-10	-13.1	+10	+5.9	+10	+1.9						
50 Normal Males (Deeds and Barnes)	+50	+11.8	-50	-14.5	+50	+7	+49	+1.3	30.8	2.8	35	1.4	+14.3	+0.8
50 Normal Females (Deeds and Barnes)	+50	+7.5	-50	-14.3	+50	+5.4	+48 level 2	+1.0	39	1.2	27.3	2.2	+9.3	+1.3
100 Normal Persons (Shanno)	+4.8		-0-23	-0-23	2-4				14	1	19	0	+7	-1
Our 100 Hypertensive Patients (Lead CF ₁)	+14.8		-9.3	-9.3	-20 diphasic 2 +78	3.84	level 85	0.5-1.5	Not known	6	Not known	1	+8	+0-1
CF ₅														
10 Normal Adults (Deeds and Barnes)	+10	+19.3	-10	-7.0	+10	+4.8	+8	+0.7						
50 Normal Males (Deeds and Barnes)	+50	+16.4	-50	-7.4	+50	+5.4	+40	+0.7	35	4.7	22	1.8	+12.0	+0.7
50 Normal Females (Deeds and Barnes)	+50	+12	-46 +4	-5.8	+50	+4.7	level 8 +33 -6 level 11	+0.5 -0.3	24.9	1.8	18.7	8.6	+8.9	+1.2
100 Normal Persons (Shanno)	+4.8		-0-23	-0-23	1-4				20	2	12	0	+6	+8
Our 100 Hypertensive Patients	+15.2		-2.3	-2.3	diphasic 2 -33 +65	2.25	level 79	-0.5 to -2.5	Not known	5.5	11	0	+4	+0

the systolic pressure 160 mm. or more in ninety-eight cases, the upper limits being 270 systolic and 160 diastolic. Eye-ground changes and renal biopsies varied from normal to Grade 4 according to the system of grading described previously in this paper. Heart size as determined by x-ray examination ranged from normal through hearts which had a slightly prominent or rounded ventricle to hearts which showed definite enlargement by measurement.

The work of Deeds and Barnes²⁶ who studied the precordial leads in 110 normal adults between the ages of 21 and 33 years and that of Shanno²⁷ who analyzed them in one hundred normal student nurses have been utilized to give some control standards for comparison, and their average values are recorded with ours in Table XII. Their IVF lead is not always comparable to our Lead CF₄ but was included since a great number of the hearts in our series were not enlarged, and Lead IVF and Lead CF₄ would then coincide.

QRS WAVES IN THE PRECORDIAL LEADS OF THE ENTIRE SERIES

In our series of one hundred cases the voltage of the QRS complexes varied a great deal, and an accurate average was impossible to obtain because the string went off the film often when the voltage was high. However, when exact measurements were possible, as they were in the great majority of cases, the average height of the R wave in Lead CF₂ was 4.1 mm., in Lead CF₄ 14.8 mm., and in Lead CF₅ 15.2 millimeters. In four cases the R wave was absent in Lead CF₂, and in one case it was absent in Leads CF₂, CF₄, and CF₅ so that the tracing suggested the presence of an old anterior myocardial infarction although there was no history of one. These figures can be compared with those of Deeds and Barnes²⁶ whose findings were as follows: the average amplitude of the R wave in Lead CF₂ was 8.4 mm. in males and 4.6 mm. in females; in Lead IVF it was 11.8 mm. in males and 7.5 mm. in females; and in Lead CF₅ it was 16.4 mm. in males and 12 mm. in females. In Shanno's series²⁷ it was 4 to 7 mm. in Lead CF₂, 4 to 8 mm. in Lead IVF, and slightly more than the average of Lead IVF in Lead CF₅. The average amplitude of the S wave in our series was 20.6 mm. in Lead CF₂, 9.3 mm. in Lead CF₄ and 2.3 mm. in Lead CF₅. These findings can be compared with those of Deeds and Barnes and of Shanno which were as follows: Deeds and Barnes gave the average amplitude of the S wave in Lead CF₂ as 25.4 mm. in males and 24.5 mm. in females, in Lead IVF as 14.5 mm. in both males and females, and in Lead CF₅ as 7 mm. in males and 7.4 mm. in females; Shanno obtained an average amplitude of 19 to 22 mm. in Lead CF₂, 0 to 23 mm. in Lead IVF, and slightly less than that in Lead CF₅.

We considered any voltage of the R wave or the S wave of 25 mm. as borderline, and any of 25 to 30 mm. or over as high. The duration of the QRS complexes varied from 0.07 to 0.11 second with the greatest number measuring 0.08 second.

The RS-T segment in Lead CF₂ was elevated in seventy-seven instances; the deviation from the base line varied from 0.5 to 3.5 millimeters. The RS-T segment in Lead CF₄ was elevated only fifteen times, the deviation varying from 0.5 to 1.5 millimeters. The RS-T segment in Lead CF₅ was depressed from 0.5 to 2.5 mm. in twenty-one instances.

T WAVES IN THE ENTIRE SERIES

The average height of the T waves in Lead CF₂ was 5.02 millimeters. This figure is very close to the average amplitude of the normals of Deeds and

Barnes who found it 4.3 mm. in females and of Shanno who found it from 1 to 4 millimeters. However, the average amplitude of the T waves in Lead CF_2 in Deeds and Barnes' series of 50 males was 7.1 mm., the maximal T wave being 15.5 mm. and the minimal T wave 3 mm. The highest in our series was 11 mm., and it seemed to us from our study that any T wave 7 mm. or more in amplitude might be called relatively high. The lowest T wave in Lead CF_2 in our series was 1 mm. in height.

The average amplitude of the positive T waves in Lead CF_4 was 3.84 millimeters. This average is in accord with the average of 2 to 4 mm. which Shanno found in Lead IVF but lower than the 7 mm. in fifty males and the 5.4 mm. in fifty females which Deeds and Barnes found. The highest in our series was 8 mm. as compared to a maximal T wave of 14.3 mm. in Deeds and Barnes' series of fifty males, 9.3 mm. in their series of fifty females, and 7 mm. in Shanno's series. In this lead also we recorded any T wave which was 7 mm. or more in amplitude as relatively high.

The average amplitude of the positive T waves in Lead CF_5 was 2.25 millimeters. This average is again in agreement with the findings of Shanno who gives the average amplitude in this lead as 1 to 4 mm.; and again the figures of Deeds and Barnes are higher, being 5.4 and 4.7 mm. for males and females, respectively, with maximal T waves of 12 and 8.9 millimeters. The highest T wave in our series was 4 mm., and again the figures of Deeds and Barnes are higher, being 5.4 and 4.7 mm. for males and females, respectively, with maximal T waves of 12 and 8.9 millimeters. We considered any T wave which was only 1 mm. in amplitude as borderline and any which was less than 1 mm. definitely abnormal.

NORMAL T WAVES

Fifty of our one hundred precordial electrocardiograms were within normal limits as to T waves, but because of the presence of some changes which we thought noteworthy we subdivided the group as follows: in thirty-four cases the T waves were normal and the precordial leads probably within normal limits. In twelve cases we found no distinct T-wave abnormalities but noted that the amplitude of the T wave in Lead CF_2 was relatively high, and in four cases there was an unusually high T wave in Leads CF_2 and CF_4 . Eight of the cases with no T-wave changes, four of the twelve cases showing relatively high T waves in Lead CF_2 , and three of the four cases showing relatively high T waves in both Leads CF_2 and CF_4 had in addition rather high voltage of the QRS complexes in one or more of the three precordial leads.

Forty-one of the fifty cases with normal precordial leads also showed normal limb leads except for left axis deviation which appeared in twenty-one cases. Subdividing these as we have already mentioned we found the following: in twenty-nine of the thirty-four cases showing normal precordial leads as to T waves, the limb leads were normal except for left axis deviation which occurred in seventeen cases; ten of the twelve cases showing unusually high T waves in Lead CF_2 had normal limb leads except for left axis deviation in three, and two of the four cases showing unusually high T waves in Leads CF_2 and CF_4 had normal limb leads except for left axis deviation in one. In Fig. 1 there is an electrocardiogram representative of this group of normal precordial leads in hypertensive patients; it shows no T-wave abnormalities.

ABNORMAL T WAVES

In fifty of our one hundred cases we found some definite abnormalities in the precordial T waves. In thirteen cases T-wave changes (including low T in eight, diphasic T in one, and inverted T in four cases) occurred only in Lead CF_5 ; in three of these cases there was also unusually high voltage of the QRS complexes in one or more leads. In ten cases there were T-wave changes in both Lead CF_2 and Lead CF_5 as follows: very high T in Lead CF_2 with low T in Lead CF_5 in three cases; very high T in Lead CF_2 with inverted T in Lead CF_5 in six cases; and a low T wave in Lead CF_2 with an inverted T wave in Lead CF_5 in one case. In one instance there was a rather high T wave in Lead CF_4 with a low T wave in Lead CF_5 , and in one there was a relatively high

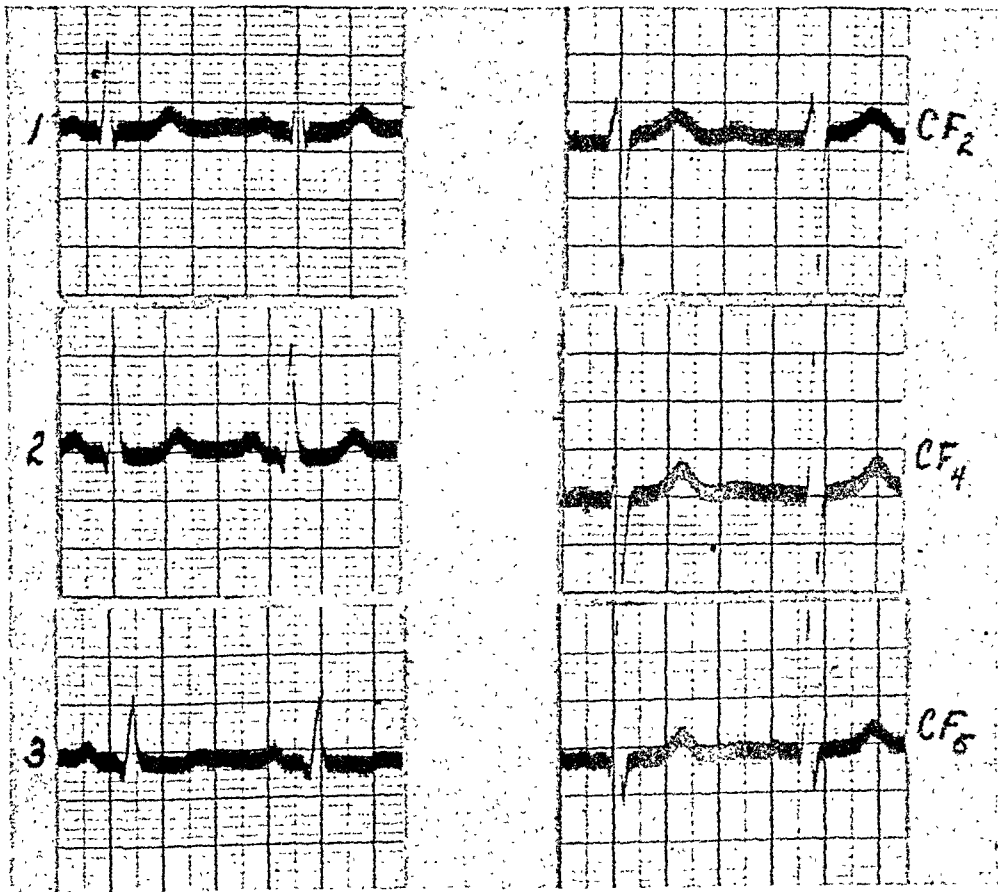


Fig. 1.—H. V., a woman, aged 52 years. Electrocardiogram taken March 22, 1944; blood pressure, 200/100. Normal record (both limb and precordial leads).

T wave in Leads CF_2 and CF_4 with borderline low T in Lead CF_5 . Thus, there were important T-wave changes in Lead CF_5 in twenty-five of our fifty abnormal precordial leads, and in seventeen of these twenty-five the limb leads were also abnormal. In fact, as was to be expected, the T wave in Lead CF_5 often resembled that in Lead I. Figs. 3, 4, and 5 show electrocardiograms which are characteristic of some of the ones seen in this group; the T wave in Lead CF_5 is inverted.

In fifteen of the one hundred cases there were changes in the T waves in both Leads CF_4 and CF_5 as follows: inverted T in Leads CF_4 and CF_5 in eleven cases; low T in Lead CF_4 and inverted T in Lead CF_5 in two cases; and inverted T in Lead CF_4 and low T in Lead CF_5 in two cases. In thirteen of these fifteen cases the limb leads were abnormal. In ten cases there were changes in Lead CF_2 in addition to the abnormalities of the T waves in Leads

CF_4 and CF_5 as follows: four cases showed very high T waves in Lead CF_2 and inverted T waves in Leads CF_4 and CF_5 ; one showed low T waves in Leads CF_2 , CF_4 , and CF_5 ; three showed very high T waves in Lead CF_2 , low or diphasic T waves in Lead CF_4 , and inverted T waves in Lead CF_5 ; and one showed low T waves in Lead CF_2 and inverted T waves in Leads CF_4 and CF_5 . Six of the ten cases had, in addition to T-wave abnormalities, very high voltage of the QRS complexes in one or more leads. Nine of the ten had abnormal limb leads, eight with abnormal T_1 and T_2 , and one with only a borderline low T_1 .

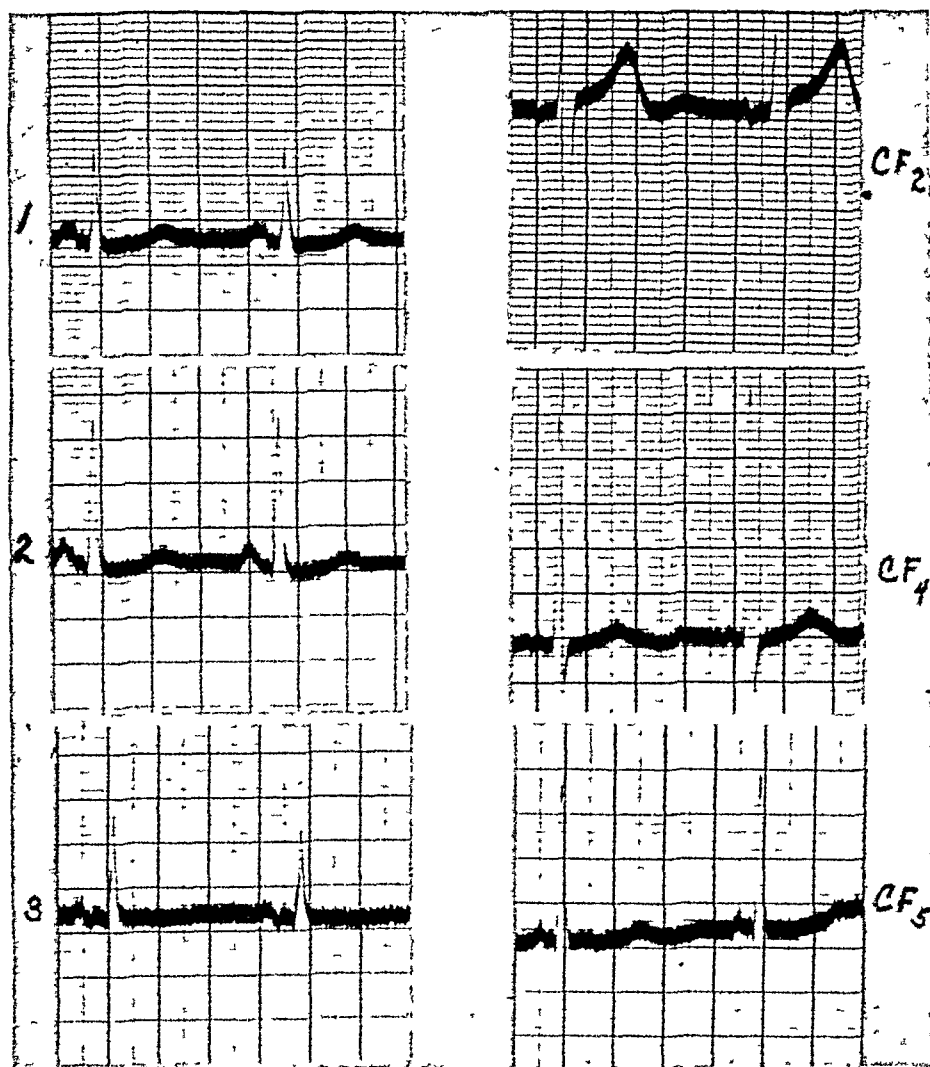


Fig. 2.—M. N., a woman, aged 56 years. Electrocardiogram taken Nov. 27, 1944; blood pressure, 190/110. Electrocardiogram showing slight depression of S-T segments in Lead I and low T waves in the limb leads and in Leads CF_4 and CF_5 .

Thus, in twenty-five of our one hundred cases there were important T-wave abnormalities in Leads CF_4 and CF_5 . This group is represented by the electrocardiogram shown in Fig. 6 which has inverted T waves in Leads CF_4 and CF_5 . In Fig. 5 there is presented a tracing which is characteristic of those seen in moderately advanced hypertensive heart disease and in Fig. 6 a tracing such as is seen in far-advanced cases.

CORRELATIONS

In Table XIII the T-wave changes in the precordial leads are correlated with the height of the diastolic blood pressure. In general it may be said that

TABLE XIII. T-WAVE CHANGES IN THE PRECORDIAL LEADS CORRELATED WITH DIASTOLIC BLOOD PRESSURES

DIAS- TOLIC B.P.	NUM- BER OF ECG'S	NORMAL PRECORDIAL LEADS T-WAVE CHANGES			ABNORMAL PRECORDIAL LEADS T-WAVE CHANGES				TOTAL ABNOR- MAL
		NONE	IN CF ₂	IN CF ₂ AND CF ₄	IN CF ₅	IN CF ₄ AND CF ₆	IN CF ₂ , 4, 5	IN CF ₂ AND CF ₅	
91-120	47	18 (38.3%)	7 (14.9%)	2 (4.2%)	8 (17%)	6 (12.8%)	4 (8.5%)	2 (4.2%)	20 (42.5%)
121-140	44	15 (34.1%)	3 (6.8%)	1 (2.2%)	7 (15.9%)	11 (25%)	3 (6.8%)	4 (9.1%)	25 (56.8%)
Over 140	9	1 (11.1%)	1 (11.1%)	0 (0%)	0 (0%)	0 (0%)	3 (33.3%)	4 (44.4%)	7 (77.7%)

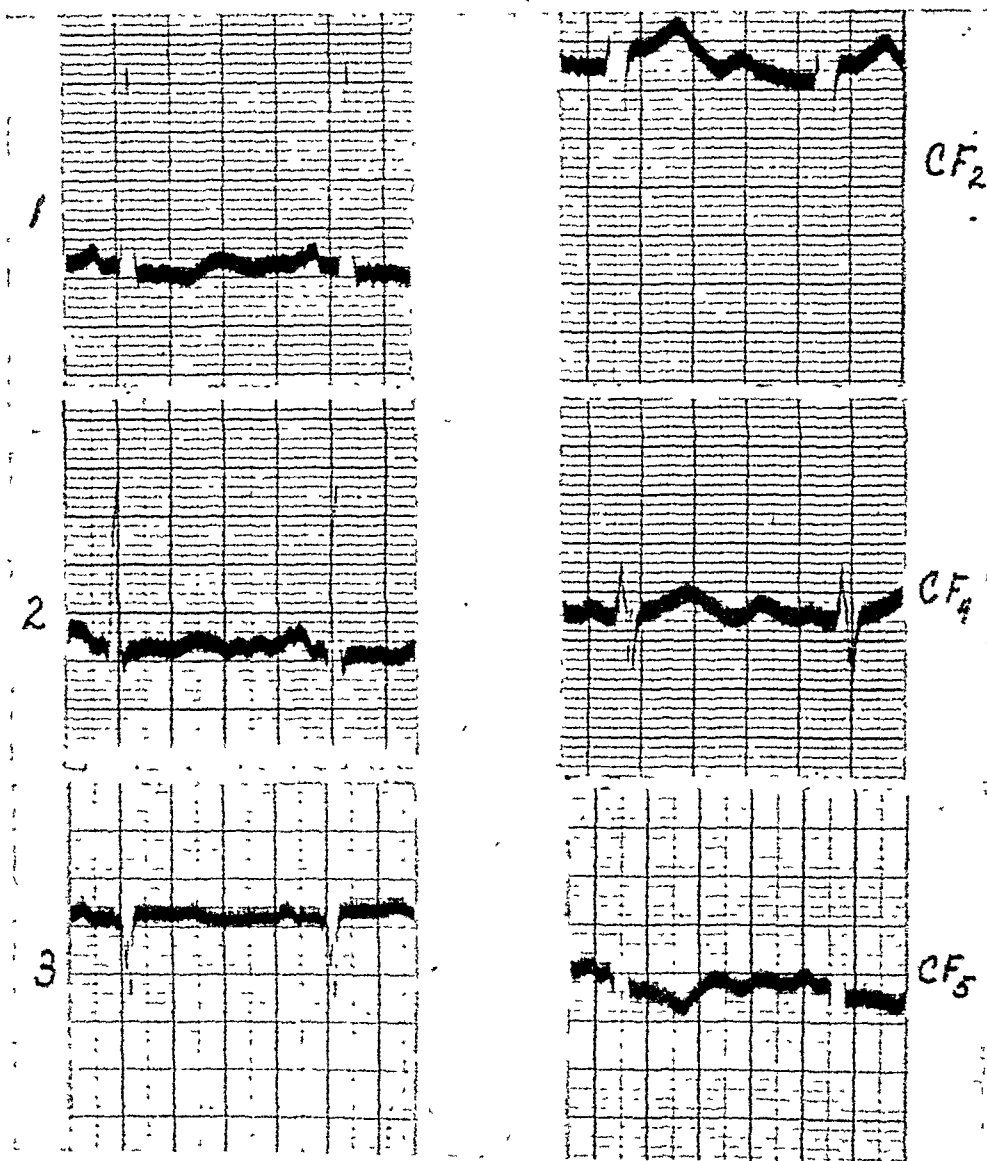


Fig. 3.—M. M., a woman, aged 49 years. Electrocardiogram taken Sept. 29, 1943; blood pressure, 270/122. Hypertensive pattern with depression of S-T segments in Leads I and II, slightly inverted T waves in Leads I, II, and CF₂, prominent U waves in Leads CF₂ and CF₄, and inverted U waves in CF₂.

the percentage of abnormal precordial leads is greater in the groups which have the highest diastolic blood pressures.

In Table XIV the T-wave changes in the precordial leads are correlated with the duration of hypertension. The histories given us as to the duration of hypertension were quite unreliable since it was an accidental and incidental finding in many cases. So it is not surprising that there is little correlation between the electrocardiogram and the known duration of hypertension.

In Table XV the T-wave changes in the precordial leads are correlated with the heart size. Contrary to our findings in the limb leads, a much larger

TABLE XV. CORRELATION OF T-WAVE CHANGES IN THE PRECORDIAL LEADS WITH THE HEART SIZE

SIZE	NUM- BER OF ECG'S	NORMAL PRECORDIAL LEADS T-WAVE CHANGES			ABNORMAL PRECORDIAL LEADS T-WAVE CHANGES				TOTAL ABNOR- MAL
		NONE	IN CF ₂	IN CF _{2, 4}	IN CF ₂	IN CF _{2, 3}	IN CF _{4, 5}	IN CF _{2, 4, 5}	
Normal	28	18 (64.3%)	2 (7.1%)	1 (3.6%)	6 (21.4%)	0	1 (3.6%)	0	7 (25%)
Promi- nence of left ven- tricle or rounded apex	41	9 (22%)	6 (14.6%)	1 (2.4%)	8 (19.5%)	6 (14.6%)	9 (22%)	2 (4.9%)	25 (60.9%)
Enlarged	20	5 (25%)	2 (10%)	0	1 (5%)	3 (15%)	4 (20%)	5 (25%)	13 (65%)

TABLE XVI. CORRELATION OF T-WAVE CHANGES IN PRECORDIAL LEADS WITH EYE-GROUND CLASSIFICATION

EYE GROUNDS	NUM- BER OF ECG'S	NORMAL PRECORDIAL LEADS T-WAVE CHANGES			ABNORMAL PRECORDIAL LEADS T-WAVE CHANGES				TOTAL ABNOR- MAL LEADS
		NONE	IN CF ₂	IN CF _{2, 4}	IN CF ₂	IN CF _{2, 3}	IN CF _{4, 5}	IN CF _{2, 4, 5}	
N	15	8 (53.3%)	1 (6.7%)	0	2 (13.3%)	0	3 (20.0%)	1 (6.7%)	6 (40.0%)
1	27	8 (29.6%)	6 (22.2%)	0	2 (7.4%)	5 (18.5%)	6 (22.2%)	0	13 (48.1%)
2	26	5 (19.2%)	1 (3.8%)	2 (7.7%)	3 (11.5%)	4 (15.4%)	9 (34.6%)	2 (7.7%)	18 (69.2%)
3	10	6 (60%)	1 (10%)	1 (10%)	1 (10%)	1 (10%)	0	0	2 (20%)
4	4	0	0	0	2 (50%)		1 (25%)	1 (25%)	4 (100%)

TABLE XVII. CORRELATION OF T-WAVE CHANGES IN THE PRECORDIAL LEADS WITH RENAL BIOPSIES

RENAL BIOPSY GRADE	NUM- BER OF ECG'S	NORMAL PRECORDIAL LEADS T-WAVE CHANGES			ABNORMAL PRECORDIAL LEADS T-WAVE CHANGES				TOTAL ABNOR- MAL
		NONE	IN CF ₂	IN CF _{2, 4}	IN CF ₂	IN CF _{2, 3}	IN CF _{4, 5}	IN CF _{2, 4, 5}	
0	1	1 (100%)							0 (0%)
1	4	3 (75%)					1 (25%)		1 (25%)
2	4	1 (25%)	1 (25%)		1 (25%)		1 (25%)		2 (50%)
3	16	6 (37.5%)	2 (12.5%)		2 (12.5%)	3 (18.8%)	3 (18.8%)		8 (50%)
4	1	1 (100%)							

percentage of the patients with slight or definite cardiac enlargement showed abnormal precordial leads than did those who had normal hearts by x-ray examination.

In Table XVI the T-wave changes in the precordial leads are correlated with the eye-ground classification. In general an increasing percentage of precordial leads showed abnormalities as the eye grounds showed more pathologic changes. However, there was a larger percentage of normal tracings in the group that had Grade 3 eye grounds than in any other; that is to be accounted for, doubtless by the smallness of the numbers.

In Table XVII the T-wave changes in the precordial leads are correlated with renal biopsies. We had only one patient with a Grade 4 renal biopsy who showed a normal electrocardiographic tracing. Except for that discrepancy,

a greater percentage of the precordial leads were abnormal in the cases which showed Grade 2 and 3 pathologic change than in those which showed Grade 0 to 1. The percentage of abnormal tracings was the same in the patients showing Grades 2 and 3 pathologic findings, however. These figures are not reliable since the number of renal biopsies was small.²⁵

In Table XVIII the precordial and limb leads are correlated. When the precordial leads were normal the limb leads were normal in 82 per cent of the cases and abnormal in 18 per cent of the cases. When the precordial leads were abnormal, the limb leads were abnormal in 78 per cent of the cases and normal in 22 per cent of the cases.

TABLE XVIII. CORRELATION OF NORMAL AND ABNORMAL PRECORDIAL LEADS WITH NORMAL AND ABNORMAL LIMB LEADS

PRECORDIAL LEADS	NUMBER OF ECG'S	NORMAL LIMB LEADS	ABNORMAL LIMB LEADS
Normal	50	41 (82%)	9 (18%)
Abnormal	50	11 (22%)	39 (78%)
LIMB LEADS	NUMBER OF ECG'S	NORMAL PRECORDIAL LEADS	ABNORMAL PRECORDIAL LEADS
Normal	52	41 (78.8%)	11 (21.1%)
Abnormal	48	9 (18.7%)	39 (81.3%)

Table XIX presents a correlation between the amplitude of the QRS waves and abnormalities of the T waves of the precordial electrocardiograms. There is evidently a connection between high voltage of the QRS waves in Leads CF₁ and CF₂ and abnormalities (commonly inversion) of the T waves in these same leads.

TABLE XIX. CORRELATION OF AMPLITUDE OF QRS WAVES AND OF T-WAVE ABNORMALITIES IN HYPERTENSIVE ELECTROCARDIOGRAMS

	NUM- BER	NO T- WAVE CHANGES	ABNORMAL T WAVES			
			IN CF ₂ ALONE	IN LEADS CF ₁ AND CF ₂	IN LEADS CF ₂ , CF ₄ , AND CF ₆	TOTAL NUMBER
High voltage of QRS in Leads CF ₂ , CF ₄ , and CF ₆	15	3 (20%)	4 (26.7%)	7 (46.6%)	1 (6.7%)	12 (80%)
High voltage in CF ₂	16	10	3	3	0	6 (37.5%)
In CF ₄ and CF ₆	5	1	1	3	0	4 (80%)
In CF ₄ only	2	0	1	1	0	2
In CF ₂ and CF ₄	2	2	0	0	0	0
Total	40	16	9	14	1	24

DISCUSSION

In general this study has shown that low, diphasic, or inverted T waves in Leads CF₁ and CF₂ are consistent with hypertensive heart disease. In addition, as we have indicated, high voltage of the QRS complexes in one or more of the precordial leads is a rather common finding and one to be expected, according to the work of Wilson,²⁸ in cases with left ventricular hypertrophy: "In left ventricular hypertrophy the voltage of the chief deflection of the QRS group is on the average much greater than normal, and the QRS interval is increased to 0.10 or even 0.11 second. In the leads from the right side of the precordium the R deflections are, on the average, much smaller than normal and may be absent. The transitional zone is, as a rule, much displaced to the

left. In the leads from the left side of the precordium R and often Q as well, are abnormally large; the peak of R occurs abnormally late in the QRS interval; and the T deflections are inverted." Changes in the QRS complexes in our series, aside from these changes in voltage and absent R waves in the five cases mentioned, were not outstanding. A few were notched or slurred and an occasional one was w-shaped; there was no particular widening although a few measured 0.10 to 0.11 second.

The changes in the T wave in Lead CF_2 are interesting but their significance is not clear. Low or inverted T waves in Lead CF_2 may rarely occur in normal tracings and are not necessarily an abnormal finding. The relatively high T wave seen rather frequently in this lead may perhaps be a characteristic finding in hypertensive heart disease; there is no reason to believe that it is an abnormal finding, however, and it is certainly not specific since it is seen in posterior myocardial infarction and even in normal persons. It is necessary to remember that we do not as yet have enough normal controls to know what the range of the normal amplitude of the T wave in Lead CF_2 is. There is similar uncertainty about the significance of the relatively high T wave in Lead CF_4 ; it may also occur in normal tracings and in those showing evidence of posterior myocardial infarction. Thus, again in this case, we do not know well enough the range of the normal or even the average. Elevation of the RS-T segment in Lead CF_2 of from 0.5 to 2 mm. occurs too frequently normally to be significant in our series. RS-T segment changes in Lead CF_4 were rare and not in themselves significant. Depression of the RS-T segment in Lead CF_5 appeared rather frequently, usually together with an inverted or diphasic T wave.

In correlating changes in the precordial leads with those in limb leads we found that they were usually similar, both being normal or both being abnormal in the greatest percentage of cases. In forty-one of our one hundred electrocardiograms both precordial and limb leads were within normal limits; in thirty-nine cases both showed some abnormality. Abnormal limb leads were accompanied by normal precordial leads in only nine cases, while abnormal precordial leads were accompanied by normal limb leads in eleven cases. The T waves in Lead CF_4 and CF_5 often showed abnormalities similar to those of the T waves in Leads I and II, thus supporting and confirming the evidence of cardiac involvement provided by the limb leads. Sometimes a tracing which had a borderline or questionably low T wave in Lead I and which would have to be considered within normal limits so far as the limb leads are concerned showed abnormalities in the precordial leads which make it consistent with hypertensive heart disease and lend significance to the minimal changes in the limb leads. It is true that the T-wave changes cannot be considered diagnostic since they are similar to those in coronary heart disease. However, as was mentioned in the discussion of changes in the limb leads, the early age at which the T waves become low or deeply inverted in the hypertensive patients, the fact that a number of them do revert to normal after lumbodorsal sympathectomy, and the absence of the pain of coronary insufficiency tend to rule out coronary heart disease in most instances. With the return of low and inverted T waves to normal voltage it becomes evident that the changes in many tracings which we read as consistent with hypertensive and/or coronary heart disease are to be ascribed as a rule alone to hypertensive heart disease.

From the data obtained in our study it is evident that the first changes due to hypertensive heart disease appear in the electrocardiogram in either

the limb leads or the precordial leads or both. We cannot yet determine their relative importance. However, it is clear that the changes in the precordial leads are at least as characteristic as are those in the limb leads, and we can conclude, therefore, that precordial lead electrocardiographic changes are as important and helpful in the detection of hypertensive heart disease as are changes in the limb leads, and perhaps more so.

SUMMARY AND CONCLUSIONS (B. THE PRECORDIAL LEADS)

1. Precordial Leads CF_2 , CF_4 , and CF_5 have been analyzed in the electrocardiograms of one hundred hypertensive patients upon whom preoperative studies for the Smithwick lumbodorsal sympathectomy were being done. The ages varied from 17 to 66 years with an average age of 42.4 years. The blood pressure readings ranged from 270 to 150 systolic and from 160 to 95 diastolic.

2. The precordial leads were normal as to T waves in fifty of the one hundred cases, but due to the presence of certain changes which were considered worthy of note, these fifty were subdivided as follows: in thirty-four cases they were well within the usual normal limits; in twelve cases there were unusually high T waves in Lead CF_2 ; and in four cases there were unusually high T waves in Leads CF_2 and CF_4 .

3. The QRS waves in general showed no striking abnormalities; however, R waves were absent in Lead CF_2 in four cases and in Leads CF_2 , CF_4 , and CF_5 in one case, the voltage of the R or S waves was relatively high in one or more of the three precordial leads in twenty-four cases, and there was a definite correlation between high voltage of the QRS waves and abnormalities of the T waves in Leads CF_4 and CF_5 . The R and S waves were not unusually low in any of the electrocardiograms in this series.

4. The precordial leads showed definite abnormalities of the T waves in fifty of our one hundred cases, twenty-five showing abnormal T waves in Lead CF_5 , and twenty-five showing abnormal T waves in both Leads CF_4 and CF_5 as follows: in thirteen cases T wave changes occurred only in Lead CF_5 ; in eleven cases there were changes in both Leads CF_2 and CF_5 ; in one case there were rather high T waves in Lead CF_4 with a low T wave in Lead CF_5 ; in eleven cases there were inverted T waves in Leads CF_4 and CF_5 ; in two cases there were low T waves in Lead CF_4 and inverted T waves in Lead CF_5 ; in two cases there were inverted T waves in Lead CF_4 and low T waves in Lead CF_5 ; in ten cases there were abnormalities of the T waves in Lead CF_2 as well as in Leads CF_4 and CF_5 .

5. Correlations of the T wave changes in the precordial leads with diastolic blood pressures revealed that the percentage of abnormal leads is greatest in the groups which have the highest diastolic pressure. Correlation with the known duration of hypertension was inconclusive and unsatisfactory. Correlation between heart size and the electrocardiographic changes showed a larger percentage of abnormal tracings in the group with slight or considerable cardiac enlargement than in the group with normal-sized hearts. Results from the correlations with the eye-ground changes and the renal biopsy findings were unsatisfactory. When the precordial leads were normal, the limb leads were normal in 82 per cent of the cases and abnormal in 18 per cent of the cases; when the precordial leads were abnormal the limb leads were abnormal in 78.8 per cent of the cases and normal in 21.2 per cent of the cases.

6. In general these studies have shown that low, diphasic, or inverted T waves in Leads CF_4 and CF_5 are commonly found in hypertensive heart disease.

7. In forty-one of our one hundred electrocardiograms both precordial and limb leads were within normal limits; in thirty-nine both showed some abnormality. Abnormal limb leads were accompanied by normal precordial leads in only nine cases while in eleven cases normal limb leads were accompanied by abnormal precordial leads. Hence, in 21 per cent of the cases, precordial leads showed abnormalities which would not have been noted if only limb leads had been available.

8. It is evident that the changes in the precordial Leads CF_2 , CF_4 , and CF_6 in hypertensive heart disease, although not definitely diagnostic, are as characteristic as are those in the limb leads, and we can conclude that they are equally as important and helpful in the detection of changes in hypertensive heart disease as the electrocardiographic changes in the limb leads and may uncover evidence not found in the limb leads alone.

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THE ELECTROCARDIOGRAM IN HYPERTENSION

II. THE EFFECT OF RADICAL LUMBODORSAL SYMPATHECTOMY (PRELIMINARY REPORT)

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IT IS an uncommon clinical experience to encounter patients with well-established hypertension of considerable degree who spontaneously lose their hypertension and the manifestations thereof, including characteristic abnormalities of the electrocardiogram. Over a period of twenty-five years we have faced discouragement as we have followed the generally downward course of the hypertensive cardiac patient. Three years ago a change became clearly apparent, a change that had doubtless already been going on for a few years before that, ever since the introduction of the more extensive lumbodorsal splanchnic sympathectomy for hypertension. Not only was the hypertension being controlled to a greater or lesser degree by this procedure in the majority of the patients, but the secondary cardiac manifestations, especially electrocardiographic, were also sometimes strikingly altered for the better. In other words, there was definite indication at last that, like the thyrocardiac patient of twenty years ago, the hypertensive cardiac patient was becoming amenable to improvement by surgical measures. And so this type of heart disease, too, is, to at least a certain extent, reversible if not allowed to reach an extreme and fixed status.

Improvement in the electrocardiogram following various operations for the relief of hypertension has been mentioned several times¹⁻⁵ but none of the reports has given criteria for improvement or adequate control studies, and no correlations were made. Only one gave any statistical data.⁴ The newer surgical treatment of hypertension has afforded us this opportunity not only to study postoperative changes in the electrocardiogram but to make numerous correlations between these and other changes concomitant with hypertension, including pathologic changes in the kidney. The paper that follows this will present control studies of the electrocardiogram in hypertension and its more or less natural evolution.

THE OPERATION

Briefly, the operation consists of an extensive bilateral splanchnic denervation, removal of the great splanchnic nerves from the semilunar ganglion to ap-

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proximately the mid-thoracic level, and resection of the sympathetic trunk from the ninth dorsal to the first or second and occasionally the third lumbar ganglion.

MATERIAL

A. Limb Leads.—Two hundred nine consecutive patients, upon whom lumbodorsal sympathectomies⁶ were performed by R. H. Smithwick at the Massachusetts General Hospital, were selected for study. Eighty-seven postoperative electrocardiograms were compared with the seventy-four records taken before operation on seventy-four patients who showed abnormal tracings to start with; the additional thirteen tracings were follow-up records of several of the seventy-four patients at later dates. The ages varied from 18 to 58 years with an average age of 40.1 years. The known duration of hypertension ranged from two months to twenty-four years. Eye grounds and renal biopsies varied from normal to Grade 4. The diastolic pressure on admission varied from 88 to 170 mm. of mercury. Hearts varied from normal to large by teleroentgenogram, and electrocardiograms from normal to very abnormal. The length of time after operation at which the electrocardiograms were taken ranged from two days to forty months.

None of the patients had been taking digitalis when preoperative electrocardiograms were made, but on two occasions patients were taking digitalis when tracings were made after sympathectomy.

One patient was thought to have had an acute myocardial infarction about one month before operation, and another patient was thought previously to have had a posterior myocardial infarction, but their electrocardiograms showed no evidence of such complications.

Some of the records were taken in the upright and others in the recumbent positions; in each instance, however, the postoperative electrocardiograms were taken in the same position as the respective preoperative records.

B. Multiple Precordial Leads.—During the last year and a half since we have been taking precordial electrocardiograms CF_2 , CF_4 , and CF_6 routinely on all hypertensive patients both before and after the Smithwick operation, it has become increasingly evident that they show changes as significant as those in the limb leads. The findings in these precordial leads are of diagnostic value preoperatively (see Part I of this series), and at times postoperatively they show a surprising reversal toward the normal picture. Therefore, in order to evaluate these changes a study was made of the preoperative and postoperative precordial electrocardiograms taken on forty-eight patients who have had the Smithwick lumbodorsal sympathectomy for hypertension. Patients were chosen whose preoperative tracings showed some definite abnormality in the precordial leads consistent with the diagnosis of hypertensive heart disease. In four cases the patients were on a maintenance dose of digitalis both before and after operation, but cases were omitted if they had received digitalis when the preoperative studies were done but had been taken off it before the postoperative electrocardiogram was taken, or similarly if they were given digitalis after the preoperative record was taken and kept on it postoperatively; in either instance the precordial leads would not be comparable since one set of Leads CF_2 , CF_4 , and CF_6 might show digitalis effect and the other might not.

The ages of the forty-eight patients ranged from 21 to 61 years with an average of 42.3 years. Electrocardiograms taken at varying intervals preoperatively were compared with similar ones taken from eight to twenty-eight days after operation, approximately two weeks afterward in half the cases. In

a small number of cases a more prolonged follow-up was available, and electrocardiograms taken up to a year after operation were compared with preoperative records.

In comparing the precordial leads taken before and after operation some difficulty was encountered because several technicians, taking tracings at intervals, often fail to place the electrode accurately at comparable locations on the chest for successive Leads CF_2 , CF_4 , and CF_5 . Thus Lead CF_4 in one tracing may be obviously farther to the left than the same lead in another tracing. This can often be determined by observing the relative height of the R and S waves; if the R wave in Lead CF_4 of the preoperative tracing is 10 mm. high with an S wave of 9 mm. and in the postoperative record is 5 or 6 mm. higher with a proportionately smaller S wave, we suspect that the second Lead CF_4 was probably taken farther to the left since, in the accurately taken precordial leads (except in cases of myocardial infarction), the R wave is small in CF_2 and becomes progressively higher as the electrode is moved farther out on the chest, while the S wave is deep in Lead CF_2 and becomes progressively smaller in Leads CF_4 and CF_5 . Other variations occur when inexperienced workers place the electrode in the fourth or sixth rather than the fifth intercostal space and when the patient has large or pendulous breasts. If these differences are overlooked, particularly in any comparative study, the results can be misleading. For example, if it is noted that the T wave in Lead CF_5 in a preoperative tracing is slightly inverted while in the similarly marked lead in the postoperative record the T wave is upright, the change might be interpreted as indicating improvement. However, if it is also observed that the R wave is of greater amplitude in the preoperative tracing than in the postoperative one, it is probable that the two leads were not taken exactly at the anterior axillary line and that the preoperative record with its higher R wave and slightly inverted T wave was therefore taken farther toward the left than was the postoperative record with its lower R wave. Hence the fact that the T wave is upright on the follow-up tracing may lose its significance since another Lead CF_5 taken correctly a few centimeters farther to the left might still show an inverted T wave.

POSTOPERATIVE CHANGES WHICH OCCURRED IN THE ELECTROCARDIOGRAM

A. Limb Leads.—These changes varied considerably depending upon the type and extent of the abnormality produced by the hypertension and upon the extent to which the strain on the left ventricle was relieved. Usually they were favorable, but occasionally they were unfavorable. Numerous alterations occurred in the shape of the RS-T segments, but only the significant changes will be stressed. The RS-T junction and the RS-T segment shifted in the same direction as the T waves but to a lesser degree; often the change was insignificant and difficult to measure, especially in Leads II and III. Changes in these three variables appeared to occur simultaneously although the relative change in each varied considerably in different cases. As the last portion of the RS-T segment and the first portion of the T wave in Lead I tended to become lower, flat, or even inverted during left ventricular "strain," opposite changes tended to occur after the strain was removed (Figs. 1 to 7, inclusive).

Associated with improvement in the height of the T wave in Lead I, the most frequent simultaneous alteration in Lead III was a lowering of the T wave (Figs. 1, 5, and 6). Many times an upright T wave in Lead III became inverted, as it should be normally in certain individuals (Figs. 1, 3, 4, and 7). Not uncommonly, hypertension caused a depression of the T waves in Lead III,

as well as in Lead I. Thus, if the T wave in Lead III was normally inverted, it would in some persons become more so during the "strain." In these cases, improvement consisted of elevation of the T waves in all leads (Figs. 3, 4, and 7).

Changes in Lead II were always in the same direction as those in Lead I. In the group in which improvement was associated with elevation of the T wave in Lead I and depression in Lead III, predominant changes occurred in Lead I. The T wave in Lead II, therefore, became elevated but to a lesser degree than that in Lead I, since Lead II is the algebraic sum of Leads I and III. In the group in which improvement was associated with elevation of the T waves in all leads, the T wave in Lead II became more elevated than that in Lead I for the same reason.

Improvement occurred in Lead IV, as well as in the standard leads; however, Lead IV was not included in our analyses because it was impossible to be certain that the chest electrode was at the apex in a given case, and a shift of the electrode in any direction changed the configuration of the electrocardiogram. As already noted, however, multiple precordial leads (CF_2 , CF_4 , and CF_5) were studied and the results will be presented later in this paper.

Concomitant with alterations in the T waves were changes in the electrical axis. Usually, the changes were in accord, that is, when the T wave improved, the electrical axis usually did likewise, and vice versa. Occasionally, however, improvement occurred in one while "unfavorable" changes occurred in the other.

Postoperative changes in the T waves, axis deviation, and the electrocardiogram as a whole are shown in Table I. T waves were referred to instead of RS-T segments because more striking changes occurred in the T waves. The T wave in Lead I was used in this analysis, as well as the remaining analyses, because the most consistent and usually the most marked changes occurred in the T waves in this lead. The T waves and electrical axis varied slightly from time to time, both before and after operation, and therefore standards (not stringent) were set up by which most of these minor changes could be eliminated from our statistics. In calculating the number of electrocardiograms which improved, minimal criteria were utilized on only five occasions, and only twice were electrocardiograms considered improved when there was considerable improvement in either the T wave or axis and only slight "unfavorable" change in the other (Fig. 3 is an example). The reason the electrocardiogram as a whole improved more often than the axis or T wave alone was that, not uncommonly, the T wave or axis improved while the other remained unchanged, according to our criteria.

These figures were based on analysis of all limb-lead postoperative electrocardiograms. If only tracings taken later than six months after operation

TABLE I. POSTOPERATIVE ELECTROCARDIOGRAPHIC CHANGES IN THE LIMB LEADS

NUMBER OF ECG'S	T WAVE*			AXIS		
	S	I	W	S	I	W
87	39 (44.8%)	41 (47.1%)	7 (8.1%)	50 (57.5%)	26 (29.8%)	11 (12.7%)
ECG AS A WHOLE						
	S	I	W			
87	26 (29.8%)	50 (57.5%)	11 (12.7%)			

Referring to T waves or electrical axis: S = same or no change (i.e., less than 1 mm. elevation or depression of T, or less than 15° of change in axis); I = improvement (favorable change in T or axis beyond these limits); W = worse (unfavorable change).

Referring to ECG as a whole: S = no change in T or axis; I = improvement in T or axis with no change in the other, improvement in both, or considerable improvement in one with only slight unfavorable change in the other; W = unfavorable change using same criteria.

*T wave = T in Lead I unless otherwise specified.

were considered, statistics on the electrocardiogram as a whole would have been as follows: of fifty-six electrocardiograms, seventeen (30.3 per cent) were unchanged, thirty-five (62.6 per cent) improved, and four (7.7 per cent) were worse. This may have been the more important group since possible nonspecific effects of the operation should have disappeared by the time the records were taken.

B. Multiple Precordial Leads.—Changes in the QRS complexes before and after operation were not impressive. There was no change in the shape of the complexes in the comparable leads and no difference in the length of the QRS intervals. The voltage of the R and S waves varied widely, but they did not, apparently, show any constant changes related to improvement in the T waves, and the average height of the R and S waves in the individual leads before and after operation was approximately the same. In Lead CF_2 before operation the average height of the R wave was 3.4 mm. and of the S wave 20 mm.; after operation the average height of the R wave was 6.9 mm. and of the S wave 18.1 millimeters. In Lead CF_4 the average height of the preoperative R wave of the electrocardiogram was 15.7 mm. and of the S wave 9.4 mm. as compared with 15.2 mm. and 9.2 mm. postoperatively. In Lead CF_5 preoperative measurements of the R wave averaged 16.6 mm. and of the S wave 1.9 mm., while postoperatively the averages were 14.1 and 1.9 mm., respectively.*

A few of the postoperative chest leads which showed improvement in the T waves had increased voltage, and a few had decreased voltage of the QRS complexes; the voltage of the majority remained the same. Hence the changes in the QRS complexes seem to have at present little significance in evaluating postoperative improvement.

The RS-T segments also show little constant change which can be said to indicate improvement in the postoperative tracings. The RS-T segments in Lead CF_2 in preoperative records were elevated from 0.5 to 3 mm. with an average elevation of slightly over 1 mm. in forty-five, or 94 per cent, of the cases. Similarly they were elevated from 0.5 to 4 mm. postoperatively in forty-four of forty-eight, or 91 per cent, of the cases. They were never depressed in this lead either preoperatively or postoperatively. In Leads CF_4 and CF_5 , both before and after operation, the RS-T segments were isoelectric in the majority of the cases. The number and percentages are as follows: preoperatively in Lead CF_4 they were isoelectric in thirty-six, or 75 per cent, of the cases and in CF_5 in thirty-three, or 69 per cent, of the cases; postoperatively they were isoelectric in CF_4 in twenty-nine, or 59 per cent, of the cases and in CF_5 in thirty-eight, or 79 per cent, of the cases. They were elevated in ten preoperative and fourteen postoperative tracings in Lead CF_4 and in three preoperative and four postoperative tracings in CF_5 . They were depressed in Lead CF_4 in two cases preoperatively and in five cases postoperatively, and in Lead CF_5 in twelve cases preoperatively and in six cases postoperatively. A depression of 0.5 mm. or more in Leads CF_4 and CF_5 was usually (seventeen out of twenty-three times) associated in this series with diphasic or inverted T waves. The converse was not true, however, since inverted T waves occurred frequently with isoelectric RS-T segments. Apparently, too, the RS-T segments became isoelectric when the T waves became upright. Thus, changes in the RS-T segments apart from T-wave changes did not seem important as an indication of postoperative improvement.

As at first observed during routine readings in the Cardiac Laboratory, the T waves which are low, diphasic, or inverted in the precordial leads taken

*These results are about the same as those obtained when the R and S waves were measured in one hundred precordial electrocardiograms taken preoperatively on hypertensive patients.

TABLE II. POSTOPERATIVE ELECTROCARDIOGRAPHIC CHANGES IN THE T WAVES OF THE PRECORDIAL LEADS

NUMBER OF ECG'S	S	I					W
48	25 (52.1%)	19 (39.6%)					4 (8.3%)
		A	B	C	D	E	
		5	2	2	4	6	
		(10.4%)	(4.2%)	(4.2%)	(8.3%)	(12.5%)	

S = no change in T waves.

W = unfavorable change.

I = Definite improvement in the precordial electrocardiogram. A, marked improvement in Leads CF₁ and CF₂ with change of one or both of the T waves from inverted to upright; B, change from inverted to upright T waves in Lead CF₂; C, less deep inversion of T waves in Leads CF₁ and CF₂; D, increase in voltage in T waves in Leads CF₁ and CF₂; E, increase in voltage of T waves in Lead CF₂.

preoperatively frequently show an interesting and rather striking return toward the normal in postoperative records; we find that the changes shown are highly significant (Table II). In sixteen cases there was no change at all in the electrocardiograms taken before and after operation. To this group we added nine cases whose electrocardiograms showed such slight improvement that their significance was debatable; twenty-five of forty-eight, or 52.1 per cent. of the precordial electrocardiograms showed no noteworthy differences before and after operation.

In four, or 8.3 per cent, of the forty-eight cases the postoperative tracings became more abnormal; in one case the T wave in Lead CF₂ became 0.5 mm. lower; in two cases an isoelectric T wave in Lead CF₂ became slightly inverted; and in one case low, upright T waves in Leads CF₁ and CF₂ became deeply inverted.

In nineteen cases, or 39.6 per cent, there was clear-cut improvement in the postoperative electrocardiogram, and we subdivided this group according to the leads involved and the degree of change (Table II). In eight cases there was definite improvement of the T wave in Lead CF₂ as follows: in six cases there was an increase in voltage of from 0.5 to 1.5 mm.; in two cases there was marked improvement, inverted T waves becoming upright and of normal voltage. In eleven cases there was a definite improvement in the T waves in both Leads CF₁ and CF₂ as follows: in two cases the T waves were less deeply inverted after operation, in four cases there was an increase in the amplitude of the T waves of from 1 to 5 mm., and in five cases there was a marked change toward the normal with either one or both of the T waves, which had previously been inverted, becoming upright. One case not included in the forty-eight showed an increase in voltage of 3 mm. in the T wave in Lead CF₁ and 2 mm. in the T wave in Lead CF₂ postoperatively; the preoperative record was entirely within normal limits. Another case, also not included in the present statistical study, showed return of inverted T waves postoperatively; this electrocardiogram could not be evaluated because digitalis had been discontinued for two weeks so that some or even all of the improvement might possibly have been due to the clearing of the digitalis effect.

CORRELATIONS

In Table III postoperative limb-lead electrocardiographic changes were correlated with preoperative eye-ground findings. Criteria for grading the eye grounds were as follows: Normal, no abnormal findings in the retina; Grade 1, minimal caliber changes in the retinal arterioles; Grade 2, caliber variations

TABLE III. CORRELATION OF POSTOPERATIVE LIMB-LEAD ELECTROCARDIOGRAPHIC CHANGES WITH PREOPERATIVE EYE-GROUND CLASSIFICATION

EYE ROUNDS	NUMBER OF ECG'S	T CHANGES			AXIS CHANGES		
		S	I	W	S	I	W
Normal	1	0 (0%)	1 (100%)	0 (0%)	1 (100%)	0 (0%)	0 (0%)
Grade 1	30	18 (60.0%)	11 (36.7%)	1 (3.3%)	19 (63.3%)	6 (20.0%)	5 (16.7%)
Grade 2	24	8 (33.3%)	13 (54.2%)	3 (12.5%)	18 (75.0%)	3 (12.5%)	3 (12.5%)
Grade 3	23	11 (47.8%)	11 (47.8%)	1 (4.4%)	10 (43.5%)	11 (47.8%)	2 (8.7%)
Grade 4	9	2 (22.2%)	5 (55.6%)	2 (22.2%)	2 (22.2%)	6 (66.7%)	1 (11.1%)

	EYE GROUNDS	NUMBER OF ECG'S	ECG AS A WHOLE		
			S	I	W
	Normal	1	0 (0%)	1 (100%)	0 (0%)
	Grade 1	30	13 (43.3%)	12 (40%)	5 (16.7%)
	Grade 2	24	7 (29.2%)	13 (54.2%)	4 (16.6%)
	Grade 3	23	6 (26.1%)	16 (69.6%)	1 (4.3%)
	Grade 4	9	0 (0%)	8 (88.9%)	1 (11.1%)

with arteriovenous nicking; Grade 3, hemorrhages and exudates; Grade 4, changes as in Grade 2 plus papilledema.⁷

This table is of interest in that chances for improvement in the electrocardiogram increased as the eye grounds became worse.

TABLE IV. CORRELATION OF POSTOPERATIVE LIMB-LEAD ELECTROCARDIOGRAPHIC CHANGES WITH RENAL BIOPSIES

RENAL GRADE	NUMBER OF ECG'S	S	I	W
0	3	1 (33.3%)	2 (66.6%)	0 (0%)
1	11	5 (45.4%)	5 (45.4%)	1 (9.2%)
2	18	7 (38.9%)	8 (44.4%)	3 (16.7%)
3	28	6 (21.4%)	20 (71.4%)	2 (7.2%)
4	9	2 (22.2%)	3 (33.3%)	4 (44.5%)

In Table IV postoperative limb-lead electrocardiographic alterations were correlated with pathologic changes found in biopsy material taken from the kidneys at the time of operation. The biopsies were classified in five groups as follows: Grade 0, no abnormal findings seen; Grade 1, slight amount of vascular change (predominantly arteriolar intimal hyalinization and arterial endothelial hyperplasia); Grade 2, slightly more vascular change than in Grade 1 with an occasional hyalinized glomerulus; Grade 3, severe vascular disease in every vessel with predominant medial arteriolar hypertrophy and many hyalinized glomeruli; Grade 4, involvement of every vessel, scarring of many glomeruli, and atrophy of surrounding tubules.⁸

There appeared to be no definite correlation between postoperative electrocardiographic changes and disease in the kidneys. Only three electrocardiograms were taken on patients with normal kidneys, two of whom improved and one remained unchanged. In the group with Grade 3 kidneys, the incidence of improvement was distinctly greater and that of unfavorable change was distinctly less than in other groups. The incidence was reversed in the group with Grade 4 kidneys; however, these figures were not so statistically significant since only nine electrocardiograms were obtained in this group.

TABLE V. CORRELATION OF POSTOPERATIVE LIMB-LEAD ELECTROCARDIOGRAPHIC CHANGES WITH PREOPERATIVE HEART SIZE

HEART SIZE	NUMBER OF ECG'S	S	I	W
Normal	46	18 (39.1%)	23 (50%)	5 (10.9%)
Enlarged	38	8 (21.1%)	24 (63.2%)	6 (15.7%)

Correlations with preoperative heart size were made in Table V. The heart size in each instance was based on the roentgenologist's opinion of the tele-roentgenogram. Variations in the heart size affected slightly the chances for improvement or unfavorable change in the limb-lead electrocardiogram.

Postoperative limb-lead electrocardiographic changes were correlated with the known duration of hypertension in Table VI. The number of electrocardiograms taken in the three five-year periods, from eleven to twenty-five years, was too few to be of statistical significance, but the definite lack of correlation was evident here as it was in the two five-year periods from zero to ten years.

TABLE VI. CORRELATION OF POSTOPERATIVE LIMB-LEAD ELECTROCARDIOGRAPHIC CHANGES WITH THE KNOWN DURATION OF HYPERTENSION

DURATION (YRS.)	NUMBER OF ECG'S	S	I	W
0 to 5	52	15 (28.9%)	31 (58.8%)	6 (12.3%)
6 to 10	24	7 (29.2%)	14 (58.4%)	3 (12.4%)
11 to 15	6	3 (50%)	1 (16.7%)	2 (33.3%)
16 to 20	2	1 (50%)	1 (50%)	0 (0%)
21 to 25	1	1 (100%)	0 (0%)	0 (0%)

Table VII shows that the tendency for limb-lead electrocardiograms to improve or become worse was approximately the same in the patients with dyspnea as in those without it. Two of the four records which were taken on patients who complained of chest pain improved while the other two remained unchanged, but the number of tracings was too few to draw any definite conclusions.

TABLE VII. CORRELATION OF POSTOPERATIVE LIMB-LEAD ELECTROCARDIOGRAPHIC CHANGES WITH PREOPERATIVE SYMPTOMS

SYMPTOMS	NUMBER OF ECG'S	S	I	W
None	53	19 (37.7%)	28 (52.8%)	6 (9.5%)
Dyspnea	29	6 (20.7%)	18 (62.8%)	5 (16.5%)
Pain	4	2 (50.0%)	2 (50.0%)	0 (0.0%)

That the patient's age did not affect the incidence of change in the limb-lead electrocardiogram one way or the other is shown in Table VIII.

TABLE VIII. CORRELATION OF POSTOPERATIVE LIMB-LEAD ELECTROCARDIOGRAMS WITH THE PATIENT'S AGE

AGE (YRS.)	NUMBER OF ECG'S	S	I	W
10 to 20	1	0 (0.0%)	1 (100.0%)	0 (0.0%)
21 to 30	8	3 (37.5%)	4 (50.0%)	1 (12.5%)
31 to 40	30	7 (23.3%)	19 (63.3%)	4 (13.3%)
41 to 50	41	15 (36.6%)	21 (51.2%)	5 (12.2%)
51 to 60	6	2 (33.3%)	3 (50.0%)	1 (16.7%)

Table IX reveals that the incidence of improvement in the limb-lead electrocardiogram increased and that of unfavorable change decreased as the preoperative diastolic blood pressure became higher.

TABLE IX. CORRELATION OF POSTOPERATIVE LIMB-LEAD ELECTROCARDIOGRAPHIC CHANGES WITH DIASTOLIC BLOOD PRESSURE ON ADMISSION

B.P.	NUMBER OF ECG'S	S	I	W
100 or below	3	1 (33.3%)	1 (33.3%)	1 (33.3%)
101 to 110	17	4 (23.5%)	9 (53.0%)	4 (23.5%)
111 to 120	16	10 (62.5%)	4 (25.0%)	2 (12.5%)
121 to 130	11	4 (36.4%)	6 (54.5%)	1 (9.1%)
131 to 140	19	5 (26.3%)	13 (68.4%)	1 (5.2%)
Over 140	19	2 (10.5%)	15 (79.0%)	2 (10.5%)

Table X reveals a tendency to positive correlation between long-term improvement in the limb-lead electrocardiogram and long-term improvement in the diastolic blood pressure following sympathectomy.

TABLE X. CORRELATION BETWEEN CHANGES IN THE LIMB-LEAD ELECTROCARDIOGRAM AND THE DIASTOLIC BLOOD PRESSURE LATER THAN SIX MONTHS AFTER OPERATION

ECG	NUMBER OF ECG'S	DIASTOLIC BLOOD PRESSURE		
		S	I	W
Unchanged	17	3 (17.6%)	13 (76.5%)	1 (5.9%)
Improved	40	8 (20.0%)	29 (72.5%)	3 (7.5%)
Worse	4	1 (25.0%)	2 (50.0%)	1 (25.0%)

S = No change (using same criteria).

I = Improved (a decrease of 10 mm. Hg. when diastolic pressure is 110 or below, 15 mm. at 111 to 130, and 20 mm. over 130).

W = Worse (an increase beyond these limits).

Table XI presents the correlation between changes in the T waves of the precordial electrocardiogram and changes in the diastolic blood pressure following operation. In general there was agreement, but there were four exceptions in which the electrocardiogram became worse even though the diastolic pressure was improved postoperatively.

TABLE XI. CORRELATION BETWEEN CHANGES IN THE T WAVES OF THE PRECORDIAL ELECTROCARDIOGRAM AND THE DIASTOLIC BLOOD PRESSURE

ECG	NUMBER OF ECG'S	DIASTOLIC BLOOD PRESSURE		
		S	I	W
Unchanged	25	7 (28%)	17 (68%)	1 (4%)
Improved	19	4 (21%)	15 (79%)	0
Worse	4	0	4 (100%)	0
Total	48	11 (23%)	36 (75%)	1 (2%)

S = No change (using same criteria).

I = Improved (a decrease of 10 mm. Hg when diastolic pressure is 110 or below, 15 mm. at 111 to 130, and 20 mm. over 130).

W = Worse (an increase beyond these limits).

There was some relationship between limb-lead electrocardiographic changes and the length of time after operation at which the records were taken (Table XII). The incidence of improvement was distinctly greater and that of unfavorable change distinctly less during the second six-month period.

TABLE XII. CORRELATION OF POSTOPERATIVE LIMB-LEAD ELECTROCARDIOGRAMS WITH LENGTH OF TIME AFTER OPERATION

POSTOPERATIVE TIME	NUMBER OF ECG'S	ECG CHANGES		
		S	I	W
1 to 6 months	31	10 (32.2%)	14 (45.2%)	7 (22.5%)
7 to 12 months	23	5 (21.7%)	18 (78.3%)	0 (0%)
1 to 2 years	18	9 (50%)	8 (44.4%)	1 (5.6%)
2 to 3 years	13	3 (23.1%)	7 (53.8%)	3 (23.1%)
3 to 4 years	2	0 (0%)	2 (100%)	0 (0%)

The more abnormal the T wave in Lead I before operation, the greater the chances for its improvement after sympathectomy, as can be seen in Table XIII. When the T wave was at the borderline of normal (1 mm. or over) 35.7 per cent improved and 14.3 per cent became worse, but when it was inverted

TABLE XIII. CORRELATION OF THE HEIGHT OF THE T WAVE IN LEAD I BEFORE AND AFTER OPERATION

HEIGHT OF T ₁	NUMBER OF ECG'S	S	I	W
1 mm. or over	42	21 (50.0%)	15 (35.7%)	6 (14.3%)
Below 1 mm. but not inverted	10	3 (30.0%)	7 (70.0%)	0 (0.0%)
Diphasic to -2 mm.	21	8 (38.1%)	11 (52.4%)	2 (9.5%)
Below -2 mm.	14	3 (21.4%)	11 (78.6%)	0 (0.0%)

more than 2 mm., 78.6 per cent improved, while none became worse (the other 21.4 per cent remained unchanged).

Other preoperative electrocardiographic findings which may have influenced changes after sympathectomy were Q waves in any of the standard leads and T-wave changes in Leads II and III. One of the two patients operated upon who had abnormal Q waves in Lead I died during induction of anesthesia. In this patient the Q wave in Lead I was 2 mm. and the greatest amplitude of the RS-T deflections was 10 millimeters. The patient was thought to have died of myocardial infarction but permission for necropsy was not obtained. No follow-up electrocardiogram has been obtained on the other patient. No untoward reactions occurred in any of the fourteen patients with large Q waves in Lead III. Postoperative electrocardiograms were obtained on four of these. One Q wave of 4 mm. remained unchanged thirteen months after operation, and there were no other changes in the electrocardiogram. Another changed from a QS wave of 10 mm. to a Q wave of 7 millimeters. The axis improved but the T waves remained unchanged. In another the Q wave changed from 3.5 to 1.5 mm. without any other change in the record. The fourth electrocardiogram remained unchanged. There were no abnormal Q waves in Lead II in any electrocardiogram.

No deleterious results occurred in any of the seven patients with inverted T waves in all three limb leads or in the fourteen with inverted T waves in Leads II and III. There were no abnormal Q waves in either group.

Of the five patients with inverted T waves in all three limb leads who had follow-up tracings, the electrocardiograms improved in two (all T waves became less inverted), remained unchanged in two, and became worse in one. Of the four patients with inverted T waves in Leads II and III who had follow-up tracings, the electrocardiograms improved in three and remained unchanged in the other.

Four patients were thought to have died cardiac deaths during the period of study. One died during induction of anesthesia before operation. This was the patient already referred to whose electrocardiogram showed a Q wave of 2 mm. in Lead I with a maximal QRS deflection of 10 mm. but no other abnormality. One patient died in uremia after myocardial infarction ten days following the first-stage operation. His electrocardiogram showed a slight depression of the RS-T segment with an inverted T wave in Lead I and a diphasic T wave in Lead II. Another died three weeks postoperatively from extensive coronary disease, but no fresh infarction could be found at necropsy. The RS-T segment was slightly depressed and the T wave diphasic in Lead I. Another died from myocardial infarction with normal blood pressure two years after sympathectomy.

DISCUSSION OF INDIVIDUAL CASES

A few of the cases in which the electrocardiogram* improved (Figs. 1 to 7 and 8 to 12, inclusive) are as follows:

CASE 1.—H. L., a 31-year-old man, was admitted to the Massachusetts General Hospital on Sept. 9, 1942, because of severe hypertension discovered on a routine insurance examination four months previously. He had been having mild morning occipital headaches for two months and recently dyspnea on exertion.

On physical examination his blood pressure was found to be 165/136. Auscultation of his heart revealed early diastolic and presystolic gallop sounds, which were substantiated by sound tracings. His eye grounds were classified as Grade 1 (variation in caliber of the vessels).

*The first tracing in each instance was taken before sympathectomy. The other tracings were taken at variable intervals after operation.

Teleroentgenograms revealed some pulmonary congestion and rounding of the cardiac apex. An electrocardiogram (Fig. 1) revealed depression of the RS-T segment in Lead I with inversion of the T waves in Leads I, II, and IVF, a large QS (9 mm.) and elevation of the RS-T segment and T wave in Lead III, and slight left axis deviation.

He was given two ampules of Digifolin preoperatively. The first stage of the bilateral sympathectomy was carried out on Oct. 1, 1942, and the second stage of his operation was performed on Oct. 13, 1942. Renal biopsies showed Grade 3 chronic vascular nephritis. The gallop rhythm disappeared, his blood pressure dropped to 120/70 to 80/50, and on Nov. 3, 1942, his electrocardiogram was within normal limits. The RS-T segments had become elevated in Lead I and depressed in Lead III. The T waves had become upright in Leads I, II, and IVF and inverted in Lead III. Predominant changes occurred in Lead I, therefore, and the T wave in Lead II was elevated. Six months later he was feeling well and working hard. His blood pressure was 110/60, and his electrocardiogram was still within the range of normal. The QS in Lead III had changed to RSR'. At the end of 1944, two years after his operation, he was in good health with normal blood pressure.

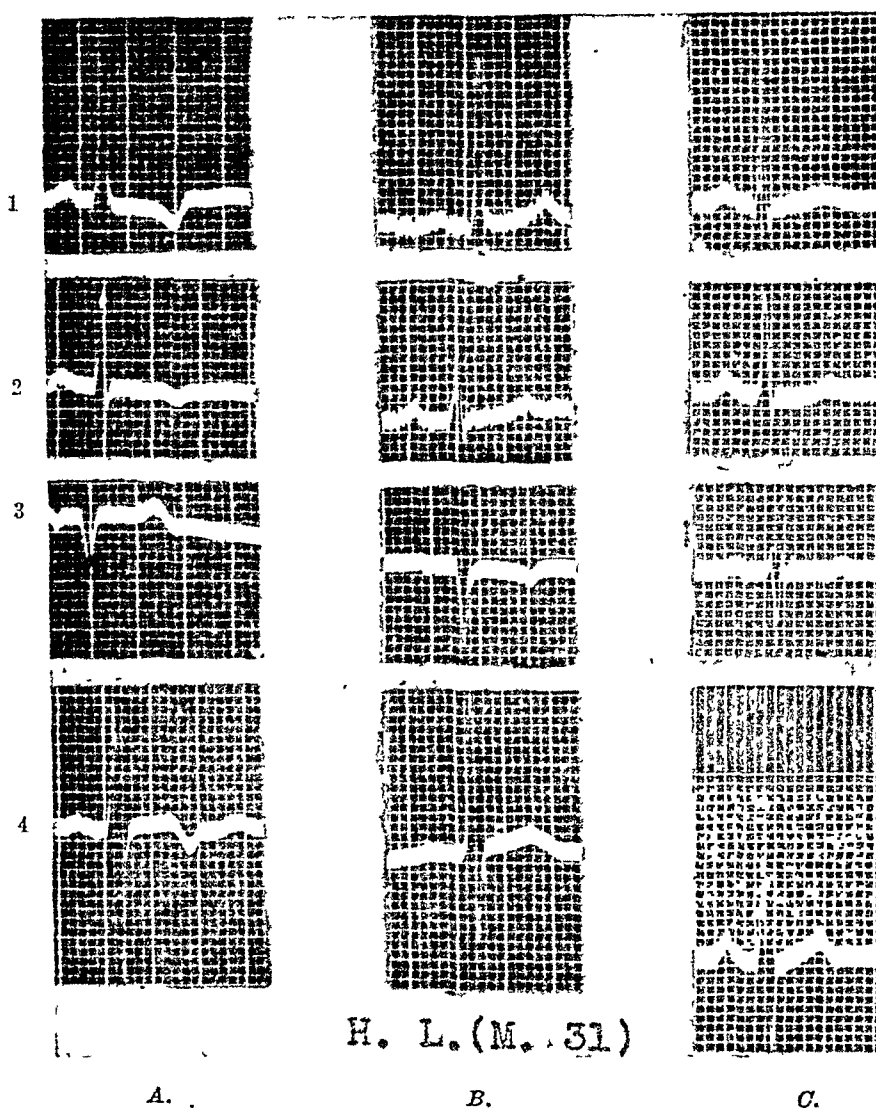


Fig. 1.—H. L., a man, aged 31 years. A, Electrocardiogram taken Oct. 9, 1942; blood pressure, 165/136. B, Taken Nov. 3, 1942; blood pressure, 120/70 to 80/50. C, Taken April 15, 1943; blood pressure, 110/60. Sympathectomy Oct. 13, 1942.

CASE 2.—L. K., a 29-year-old woman, was admitted to the Massachusetts General Hospital on Sept. 25, 1940, with a history of having had high blood pressure (up to 270/170) and headaches for two years.

On physical examination her blood pressure was found to be 240/150. Her eye grounds were classified as Grade 4 (papilledema). Her heart was not enlarged, and numerous tests were found to be within normal limits. Her electrocardiogram (Fig. 2) showed a depression of the RS-T segment and inversion of the T wave in Lead I.

The second stage of her sympathectomy was completed on Oct. 16, 1940. At the time of her postoperative check-up on Jan. 13, 1943 (twenty-eight months after operation), her blood pressure was 140/90 and her eye grounds and electrocardiogram were normal. The RS-T segments in Leads I and II and the T waves in Leads I, II, and III had become more

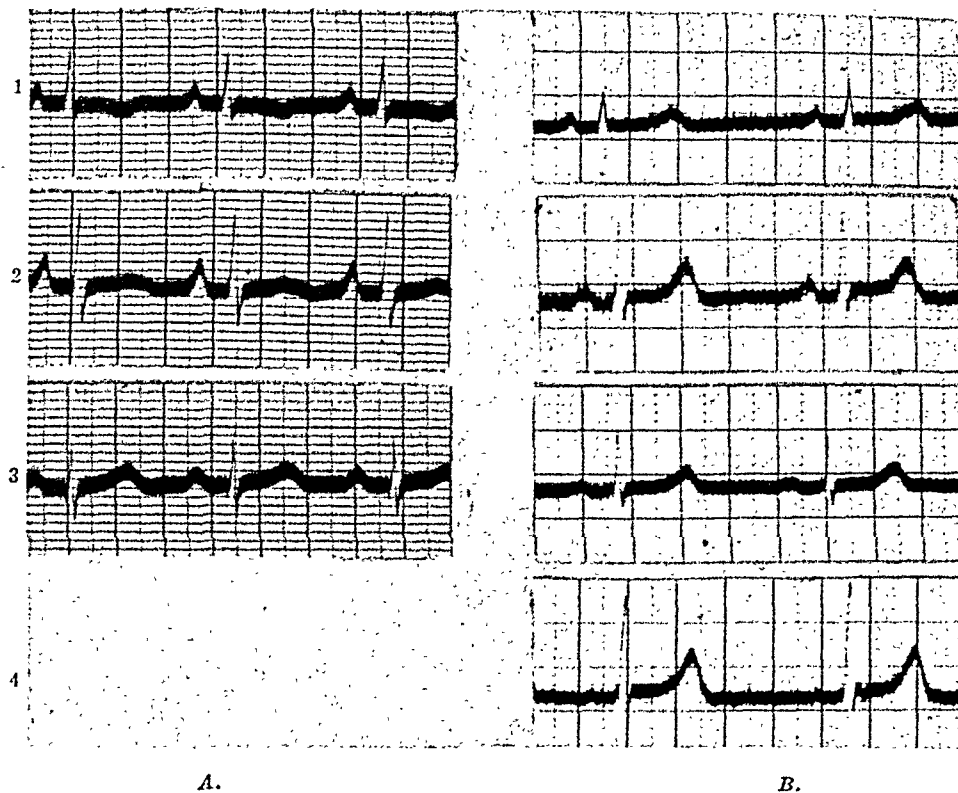


Fig. 2.—L. K., a woman, aged 29 years. A, Electrocardiogram taken Sept. 28, 1940; blood pressure, 250/140. B, Taken Jan. 13, 1943; blood pressure, 140/90. Sympathectomy Oct. 16, 1940.

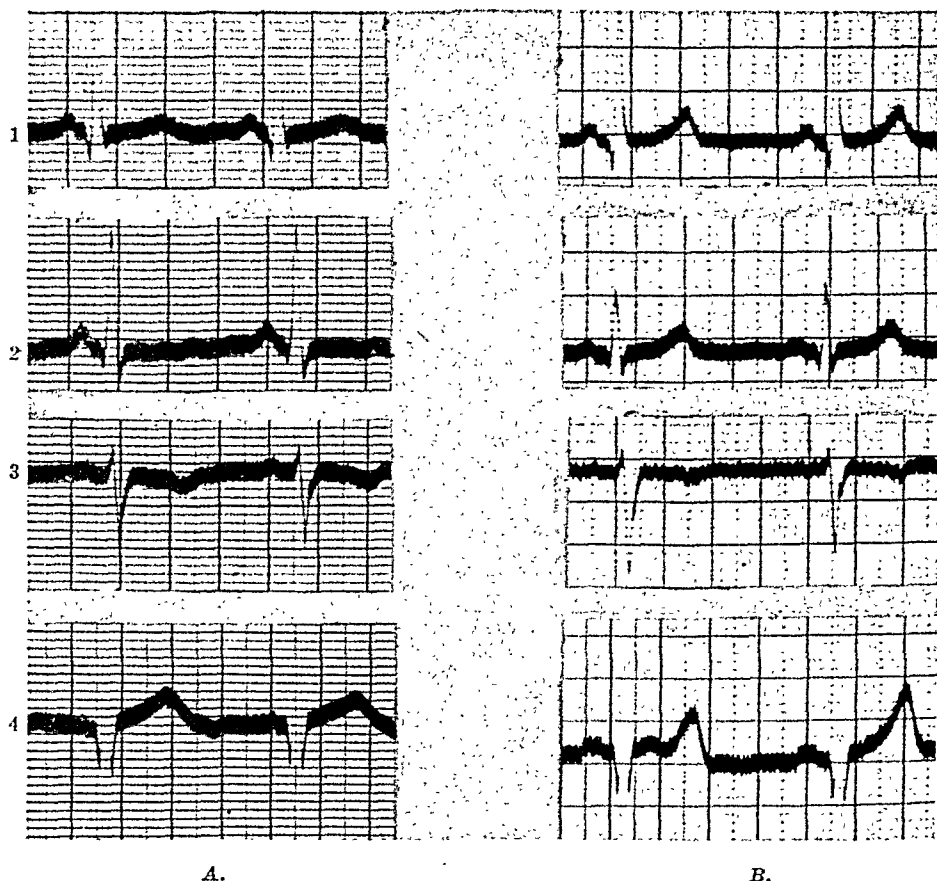


Fig. 3.—J. S., a man, aged 46 years. A, Electrocardiogram taken Dec. 6, 1940; blood pressure, 210/140 (lying), 180/135 (standing). B, Taken March 25, 1943; blood pressure, 195/145 (lying), 139/119 (standing). Sympathectomy Dec. 21, 1940.

elevated; predominant changes occurred in Lead II. There was slight improvement in the electrical axis. Ten months later, at the end of 1943, over three years after operation, the blood pressure was still normal (120/76).

CASE 3.—J. S., a 46-year-old man, who was known to have had a blood pressure of 170/110 six years previously, was admitted to the Massachusetts General Hospital on Nov. 10, 1940, with a history of having had dyspnea on exertion and dizziness for three years, and severe headaches, weakness, and blurring of vision for three weeks.

Physical examination revealed a blood pressure of 210/140, lying, and 180/135, standing. Exudates and hemorrhages were found in the eye grounds (Grade 3).

His urine contained much albumin (3 plus), many coarsely and finely granular casts, and occasional red blood cells. An intravenous phenolsulfonphthalein test showed an excretion of 5 per cent of the dye in fifteen minutes and 40 per cent in two hours. The electrocardiogram (Fig. 3) revealed slight left axis deviation, slight depression of RS-T segments, and inversion of the T waves in Leads II and III. A small Q wave (2 mm.) was present in Lead I and a slightly larger one (3.5 mm.) was present in Lead IV.

A bilateral sympathectomy was performed in December, 1940, when renal biopsies revealed Grade 3 vascular nephritis and chronic pyelonephritis.

Fourteen months after operation his blood pressure was found to be 106/60, but no electrocardiograms were taken. On March 25, 1943 (twenty-seven months after operation), his blood pressure was 195/145, lying, and 139/119, standing, and his eye grounds failed to show exudates or hemorrhages. His phenolsulfonphthalein test showed a 23 per cent excretion of the dye in fifteen minutes and 55 per cent in two hours. His electrocardiogram was within normal limits—the RS-T segments and T waves in the three standard leads had become more elevated; maximal changes occurred in Lead II. There were no changes in the Q waves. He was well and doing full-time strenuous work. Nine months later, three years after operation, his blood pressure was satisfactory, at 151/106.

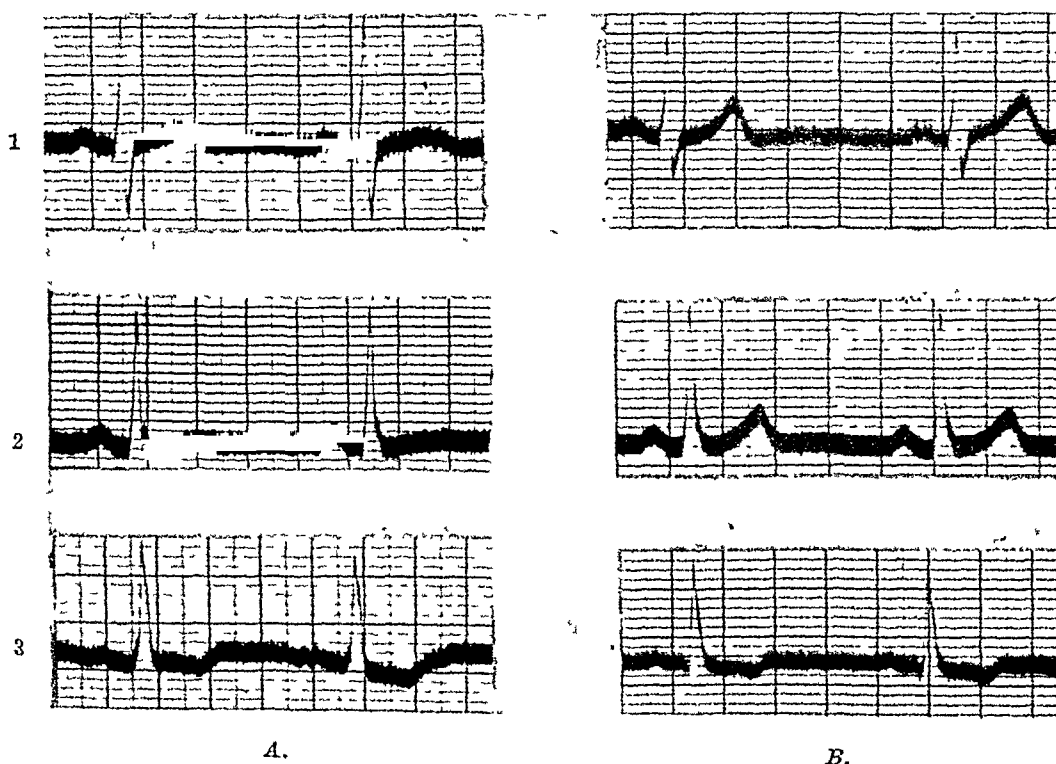


Fig. 4.—W. T., a man, aged 35 years. A, Electrocardiogram taken May 6, 1942; blood pressure, 200/145. B, Taken Nov. 2, 1942; blood pressure, 130/90. On May 3, 1943, the blood pressure was 122/76. Sympathectomy May 26, 1942.

CASE 4.—W. T., a 35-year-old man, was admitted to the Massachusetts General Hospital on May 6, 1942, with a history of having had dizzy spells for two to three years, incapacitating frontal headaches for several months, and weakness for four months. He had also had palpitation and slight dyspnea on exertion.

Physical examination revealed a blood pressure of 200/145 and Grade 2 eye grounds (a-v nicking). His heart size was at the upper limits of normal by teleroentgenogram. An electrocardiogram (Fig. 4) revealed a depression of the RS-T segment in Leads II and III with notching of the T wave in Lead II and inversion in Lead III. There was a prominent S wave in Lead I.

Six months after operation, his blood pressure was 132/76, but unfortunately electrocardiograms were not taken at that time. On May 3, 1943 (one year after operation), his blood pressure was 130/90, he was doing strenuous work, and he felt well. His electrocardiogram was now within normal limits. The RS-T segments and T waves had become more elevated in the three leads; maximal changes again occurred in Lead II.

CASE 5.—M. B., a 43-year-old woman, was admitted to the Massachusetts General Hospital on Nov. 15, 1939, because of hypertension which had been diagnosed two years previously. She had been having headaches for three to four years and blurring of vision for two years.

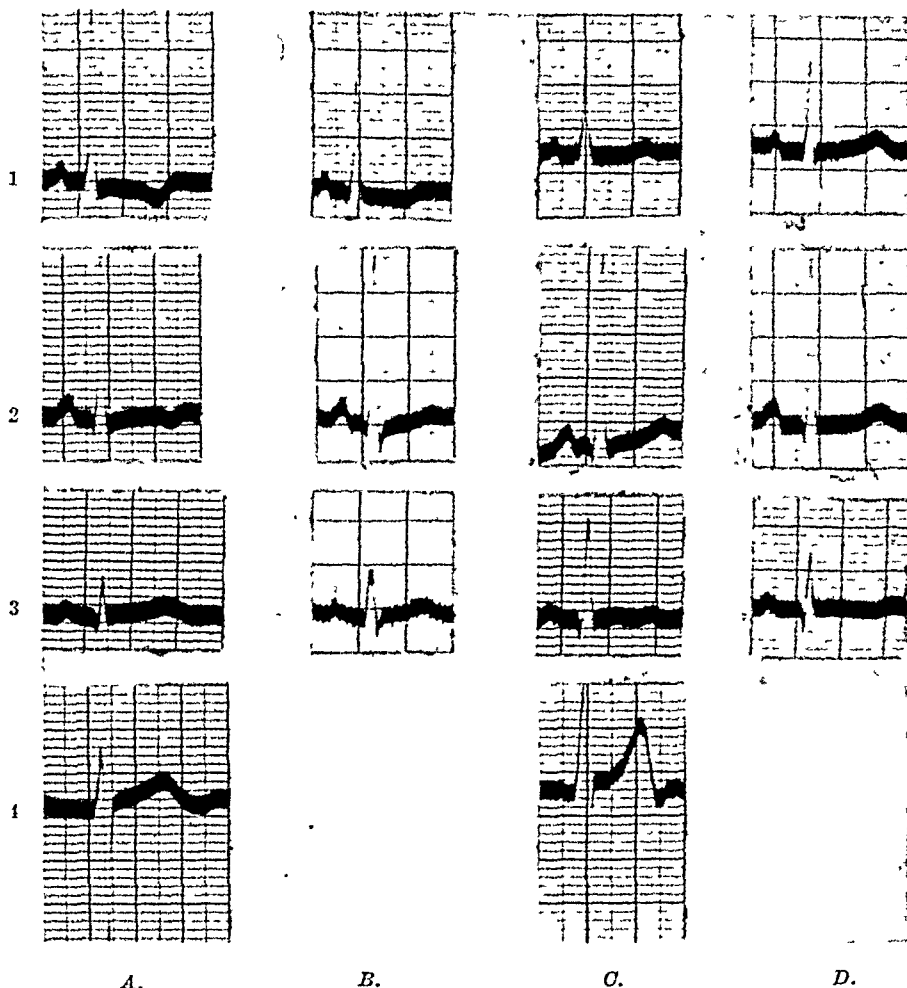


Fig. 5.—M. B., a woman, aged 43 years. A, Electrocardiogram taken Oct. 15, 1939: blood pressure, 260/110 (lying), 190/110 (standing). B, Taken Dec. 26, 1939. C, Taken Feb. 9, 1940. D, Taken Nov. 25, 1941; blood pressure, 180/110 (lying), 140/100 (standing). Sympathectomy Dec. 21, 1939.

On physical examination her blood pressure was found to be 200/110, lying, and 190/110, standing. Her eye grounds were classified as Grade 3. Teleroentgenograms revealed enlargement of the left ventricle. An electrocardiogram (Fig. 5) showed depression of the RS-T segments in Leads I and II and slight elevation in Lead III. T waves in Leads I and II were inverted.

Sympathectomy was performed on Dec. 21, 1939. The blood pressure measured 138/92 three weeks later and 177/110 two years after operation. Electrocardiograms taken five days, seven weeks, and twenty-six months, respectively, after operation showed a gradual return to normal. The RS-T segments in Leads I and II became elevated, and those in Lead III depressed. The T wave in Lead III was now inverted.

These records are of interest in that the relative postural hypotension was apparently sufficient to relieve the heart of considerable strain over a period of more than two years, as in Case 3. During this time the patient was feeling well without symptoms. Her usual pressure at home was probably well below our figures.⁹

CASE 6.—M. O., a 39-year-old woman, was admitted to the Massachusetts General Hospital on Nov. 11, 1941, with a history of having had headaches, dizzy spells, moderate dyspnea, palpitation, and occasionally substernal pain radiating down the left arm on climbing a flight of stairs, for about five months.

On physical examination her heart was slightly enlarged, her blood pressure was 180/110, and her eye grounds showed a-v nicking. An electrocardiogram revealed depression of the RS-T segments, inversion of the T waves in Leads I and II, and elevation of the T waves in Lead III (Fig. 6).

A sympathectomy was performed in March, 1942. Over thirteen months later her blood pressure was 150/100, and her electrocardiogram was almost normal. There were striking changes in the RS-T segments and axis. RS-T segments and T waves had become elevated in Leads I and II and depressed in Lead III.

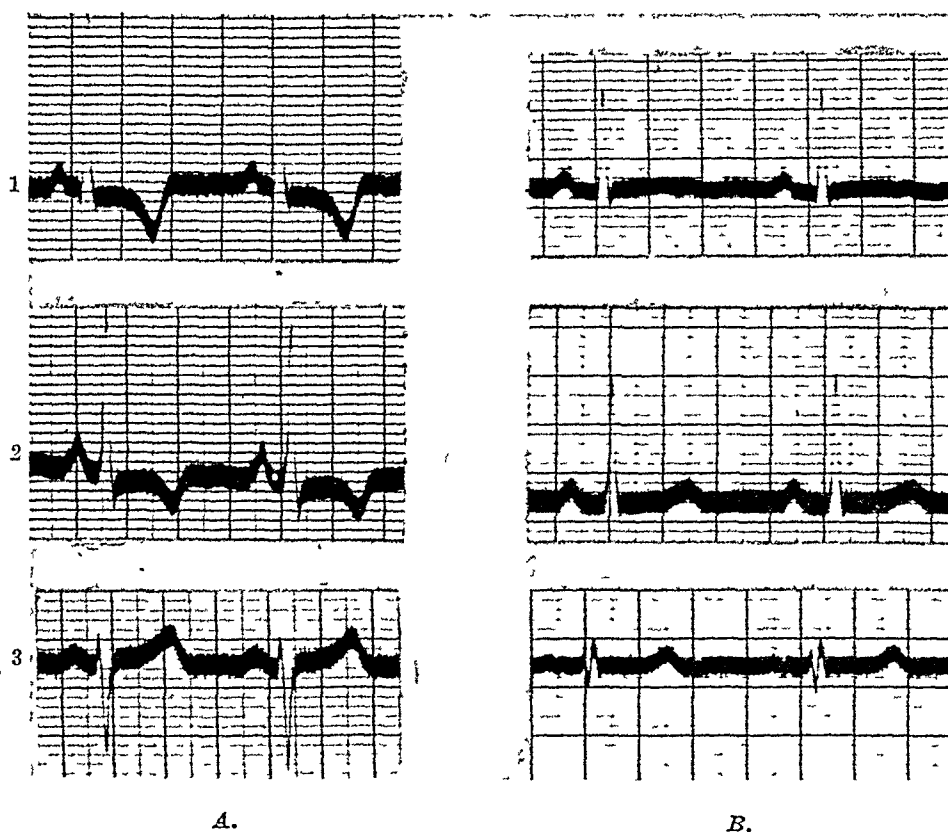


Fig. 6.—M. O., a woman, aged 39 years. A, Electrocardiogram taken Dec. 4, 1941; blood pressure, 180/110. B, Taken April 26, 1943; blood pressure, 150/100. Sympathectomy March 7, 1942.

CASE 7.—A. R., an 18-year-old man, was admitted to the Massachusetts General Hospital on Jan. 15, 1942, with a history of having had headaches for six months and palpitation, blurring of vision, mental confusion, and right facial paralysis for three days.

On physical examination his blood pressure was found to be 190/140. There was slight pulsus alternans and his eye grounds showed exudates and hemorrhages. By teleroentgenogram his heart was moderately enlarged. His electrocardiogram showed depression of the RS-T segments and inversion of the T waves in Leads II and III (Fig. 7).

A right lumbar sympathectomy and excision of a renal tumor (pheochromocytoma) were performed on Feb. 10, 1942.

On Nov. 23, 1942 (nine months after operation), he was feeling well, and his blood pressure was 116/76. His electrocardiogram was now within normal limits. The RS-T segments and T waves had become more elevated, but the T wave in Lead III was still inverted.

CASE 8.—L. H. DeW., a 35-year-old male college professor, entered the Massachusetts General Hospital in April, 1940, because of tonsillitis. His blood pressure was then normal (124/80). He re entered the hospital on May 29, 1944, because of headaches, dyspnea, and hypertension which had been discovered in 1942 at the time of an insurance examination; he was rejected on the discovery of readings of 190/130.

Physical examination at the time of his second hospital admission showed no abnormalities except for the hypertension of 190/130. Ophthalmoscopic examination showed Grade 2

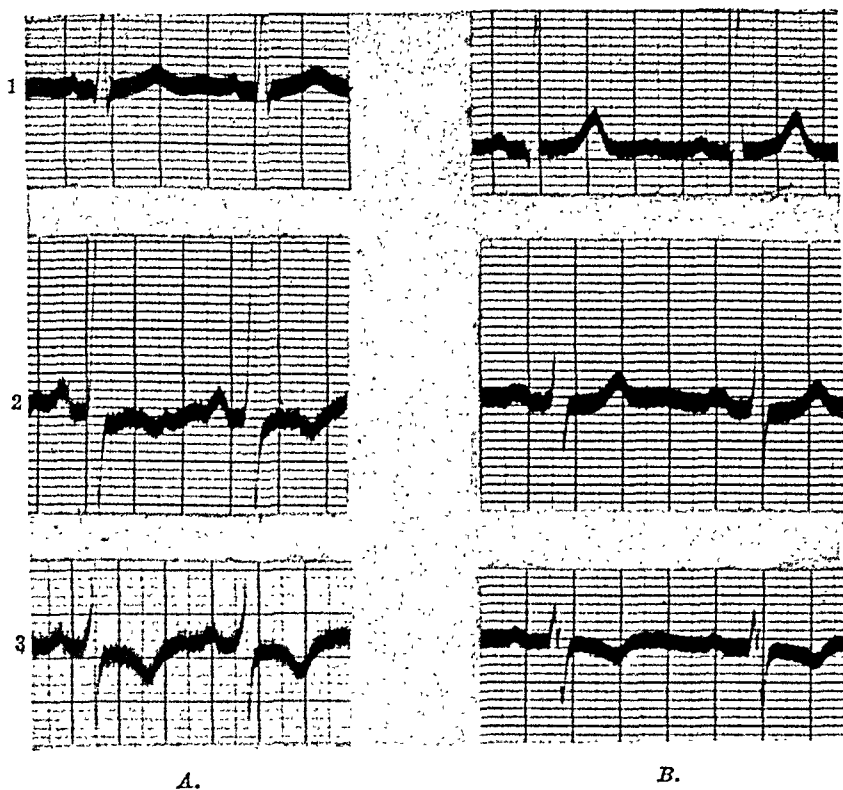


Fig. 7.—A. R., a man, aged 18 years. A, Electrocardiogram taken Jan. 20, 1942; blood pressure, 190/140. B, Taken Nov. 23, 1942; blood pressure, 110/76. Right lumbar sympathectomy and excision of pheochromocytoma, Feb. 10, 1942.

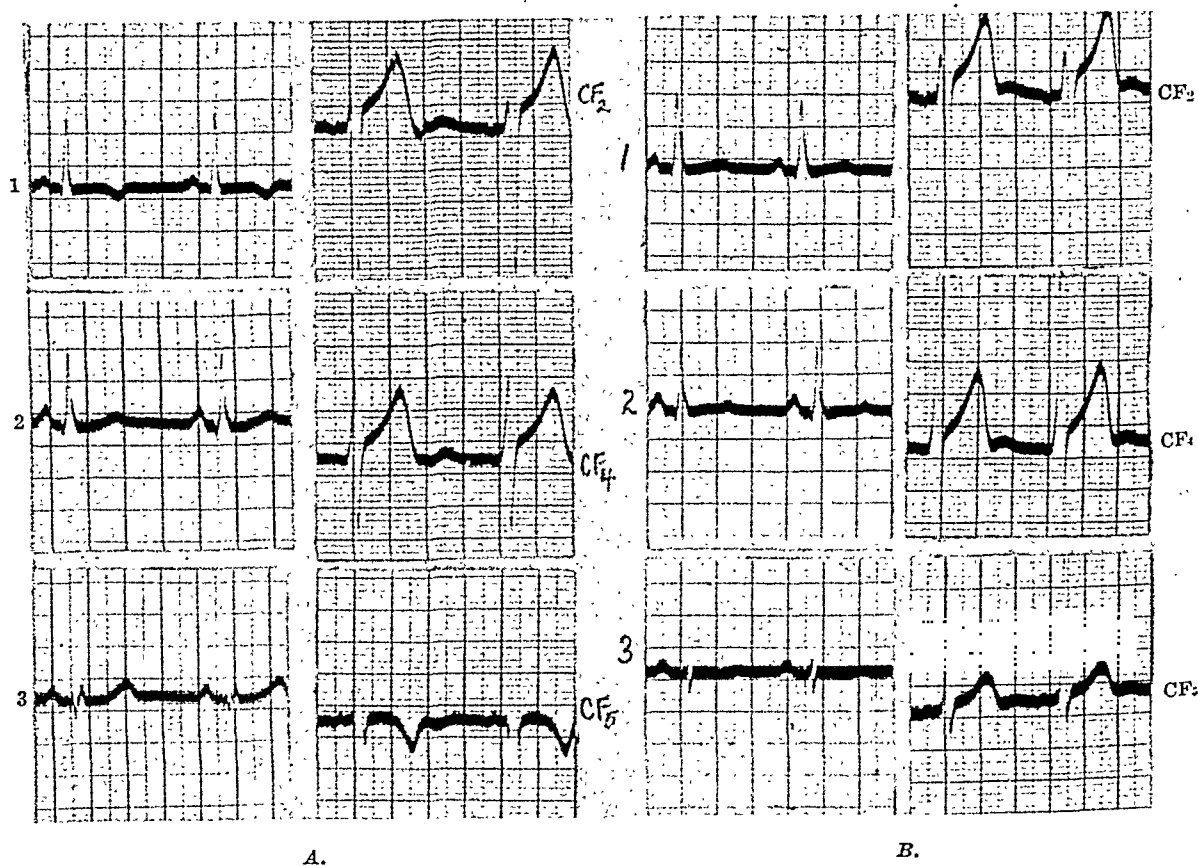


Fig. 8.—L. H. DeW., a man, aged 39 years. A, Electrocardiogram taken May 30, 1944; blood pressure 190/130. B, Taken June 21, 1944; blood pressure, 145/105. Sympathectomy May 31 and June 9, 1944.

hypertensive and Grade 3 arteriosclerotic fundi. The electrocardiogram (Fig. 8, *A*) showed normal rhythm (rate 70), normal axis, and late inversion of the T waves in Leads I and CF_1 , characteristic of "left ventricular strain." The blood was normal. The urine showed 0 to a very slight trace of albumin, with specific gravity of 1.018 to 1.024, and a few blood cells in the sediment. The renal function (phenolsulfonphthalein) test gave a reading of 62 per cent in one hour. Blood nonprotein nitrogen was 22 to 35 mg. per cent.

Bilateral lumbodorsal sympathectomy was carried out May 31 and June 9, 1944, without complications. He was discharged June 23 with a blood pressure of 130/95. His electrocardiogram (Fig. 8, *B*) taken on June 21, when his pressure was 145/105, showed normal rhythm (rate 85), with a low but upright T wave in Lead I and upright T waves in all three precordial leads—a marked improvement.

CASE 9.—M. A. W., a 50-year-old female clerk, entered the Massachusetts General Hospital, Sept. 18, 1944, because of hypertension of nine years' known duration, and right hemiplegia in the fall of 1943, which had left little residuum. There had been some dyspnea on effort.

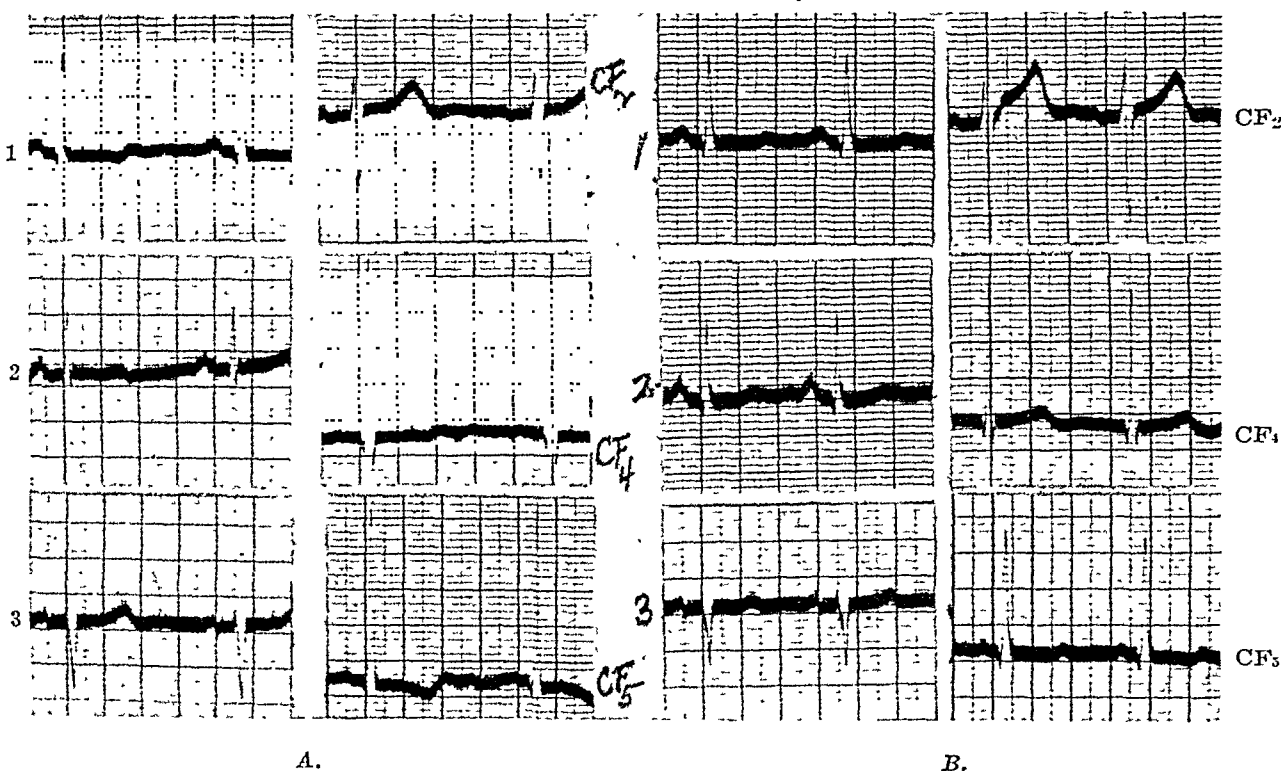


Fig. 9.—M. A. W., a woman, aged 50 years. *A*, Electrocardiogram taken Sept. 15, 1944; blood pressure, 240/130. *B*, Taken Oct. 9, 1944; blood pressure, 170/110. Sympathectomy Sept. 19 and 29, 1944.

Physical examination on admission showed nothing amiss except for slight cardiac enlargement and a blood pressure of 240/130. Ophthalmoscopic examination showed Grade 2 hypertensive and Grade 3 arteriosclerotic fundi. X-ray examination showed a heart of full size, normal aorta, and clear lungs. The electrocardiogram (Fig. 9, *A*) on Sept. 15, 1944, showed normal rhythm (rate 70), slight left axis deviation, with almost flat, diphasic T waves in Lead I, very low T waves in Leads II and CF_1 , high R waves in Leads CF_2 and CF_3 , and inverted T waves in Lead CF_4 . The blood and urine were normal. The renal function (phenolsulfonphthalein) test showed 55 per cent in one hour. Blood pressure reactions to posture, cold, and sedation were characteristic and favorable.

Bilateral lumbodorsal sympathectomy was done on September 19 and 29 without complications. She was discharged from the hospital October 20 with a blood pressure reading of 155/110. The electrocardiogram (Fig. 9, *B*) on October 9, when the pressure registered 170/110, showed normal rhythm (rate 85), very slight left axis deviation, and low but upright T waves in Leads I, CF_1 , and CF_2 —a slight but definite improvement.

CASE 10.—B. K., a 27-year-old housewife, entered the Massachusetts General Hospital Dec. 9, 1943, for hypertension which had been discovered in January, 1943. There had been no symptoms.

Physical examination on entrance to the hospital showed no abnormalities except for the hypertension (220/160). Ophthalmoscopic examination revealed Grade 2 hypertensive fundi.

X-ray examination showed apparently normal heart, lungs, and pyelogram. The electrocardiogram (Fig. 10, *A*), taken December 13, showed normal rhythm (rate 85), with normal limb leads but inverted T waves in Lead CF_4 and diphasic T waves in Lead CF_5 . The blood was normal and showed 31 mg. per cent of nonprotein nitrogen. The urine showed slight albuminuria, specific gravity up to 1.018, and a moderate number of white and red blood cells without casts in the sediment. The renal function (phenolsulfonphthalein) test registered 60 per cent in one hour.

Bilateral lumbodorsal sympathectomy was carried out on December 18 and 29 without complications. She was discharged January 18, 1944, with a blood pressure reading of 160/118. An electrocardiogram (Fig. 10, *B*) taken January 14, when the blood pressure measured 180/110, showed normal rhythm (rate 80) and normal T waves in all six leads, a distinct improvement in the precordial leads over the preoperative record.

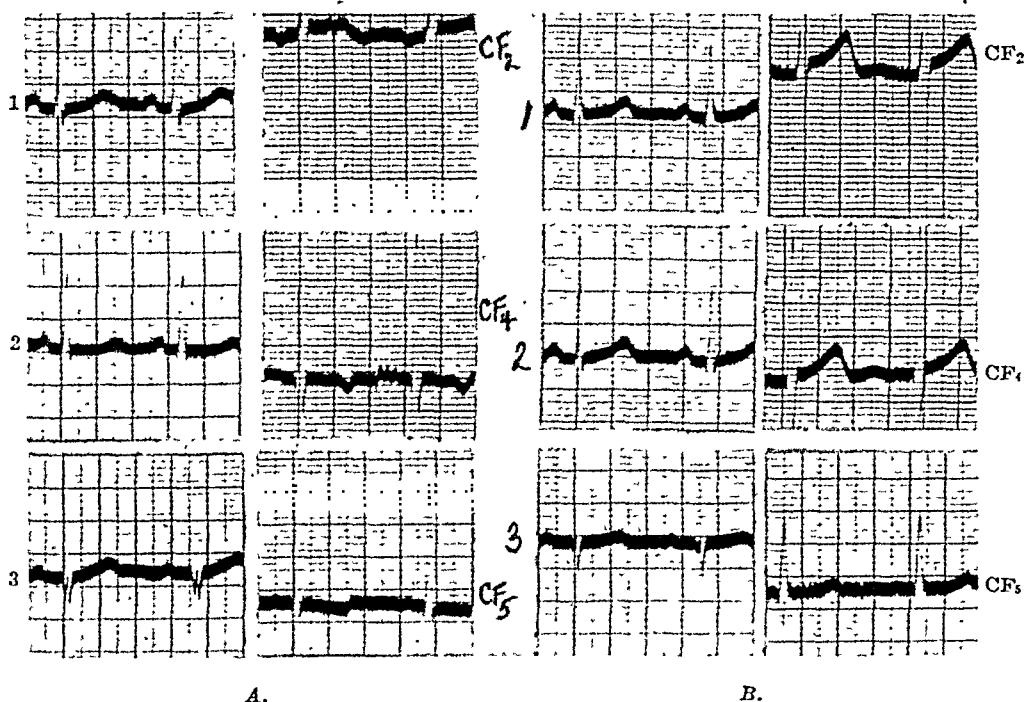


Fig. 10.—B. K., a woman, aged 27 years. *A*, Electrocardiogram taken Dec. 13, 1943; blood pressure, 220/100. *B*, Taken Jan. 14, 1944; blood pressure, 180/110. Sympathectomy Dec. 18 and 29, 1943.

CASE 11.—H. Z., a 50-year-old farmer, entered the Massachusetts General Hospital April 7, 1944, because of headaches and hypertension dating back five years. His history otherwise revealed rheumatic fever twenty-eight years before, hemorrhage from a gastric ulcer in 1939, and renal colic during the past year. There were no cardiac symptoms.

Physical examination showed no abnormalities except for hypertension (230/170), slight cardiac enlargement, and a slight apical systolic murmur. Ophthalmoscopic examination revealed Grade 2 hypertensive fundi. X-ray study showed slight enlargement of the heart, tortuous calcified aorta, clear lungs, and a normal pyelogram. An electrocardiogram (Fig. 11, *A*) taken April 10, 1944, showed normal rhythm (rate 70), slight to moderate left axis deviation, upright T waves in Lead I, almost flat T waves in Lead II, and low but upright T waves in Leads CF_4 and CF_5 . The blood and urine were normal. Serum nonprotein nitrogen was 28.5 mg. per cent. The renal function (phenolsulfonphthalein) test registered 65 per cent in one hour.

Lumbodorsal sympathectomy was carried out April 12 and 22, and the patient was discharged May 10 with a blood pressure measurement of 160/90. An electrocardiogram (Fig. 11, *B*) taken May 9, when the blood pressure registered 160/100, showed normal rhythm (rate 70), very little left axis deviation, and normal T waves in all six leads—a distinct improvement over the preoperative record.

CASE 12.—E. V. H., a 44-year-old male physician, entered the Massachusetts General Hospital Aug. 1, 1944, for study and treatment of hypertension of three years' duration. His blood pressure, previously normal, was found to register 165, systolic, and 120 to 130, diastolic, in 1941, when he was examined because of the onset of headaches. Since that time

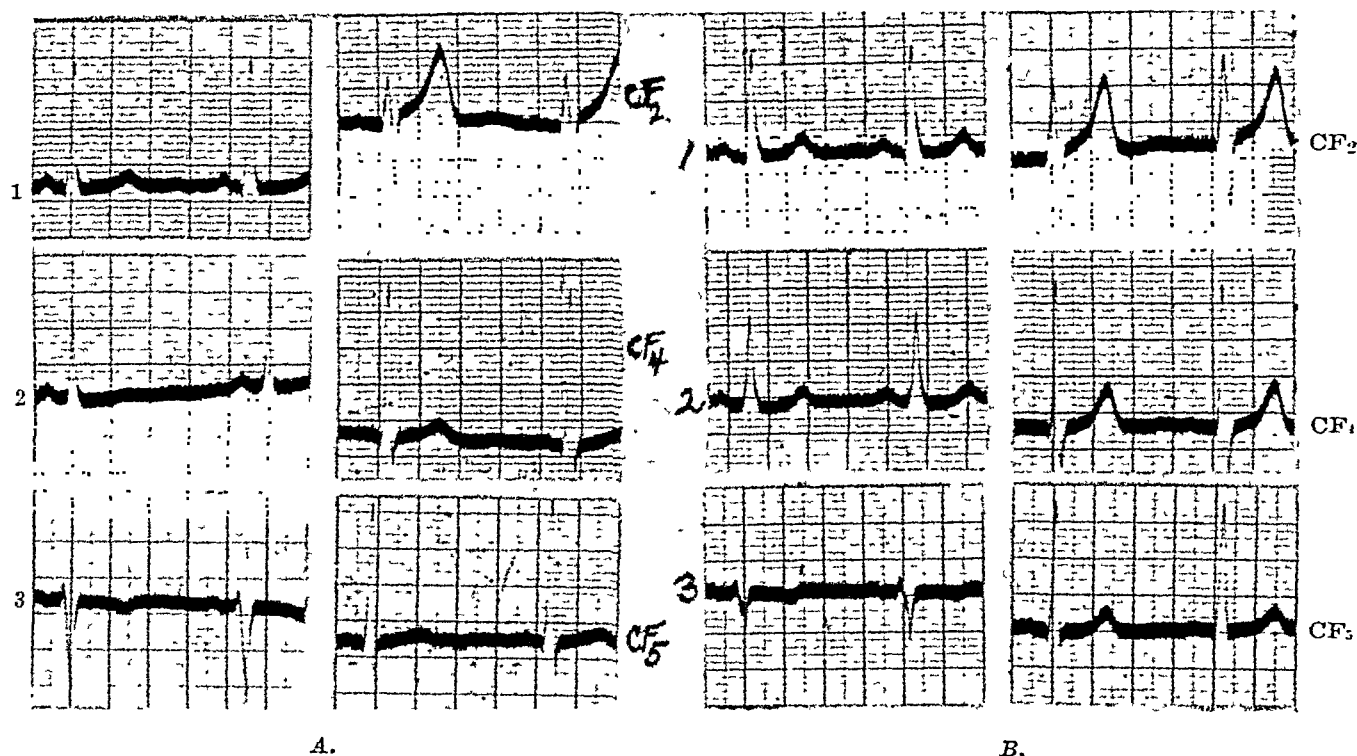


Fig. 11.—H. Z., a man, aged 50 years. A, Electrocardiogram taken April 10, 1944; blood pressure, 225/130. B, Taken May 9, 1944; blood pressure, 160/100. Sympathectomy April 12 and 22, 1944.

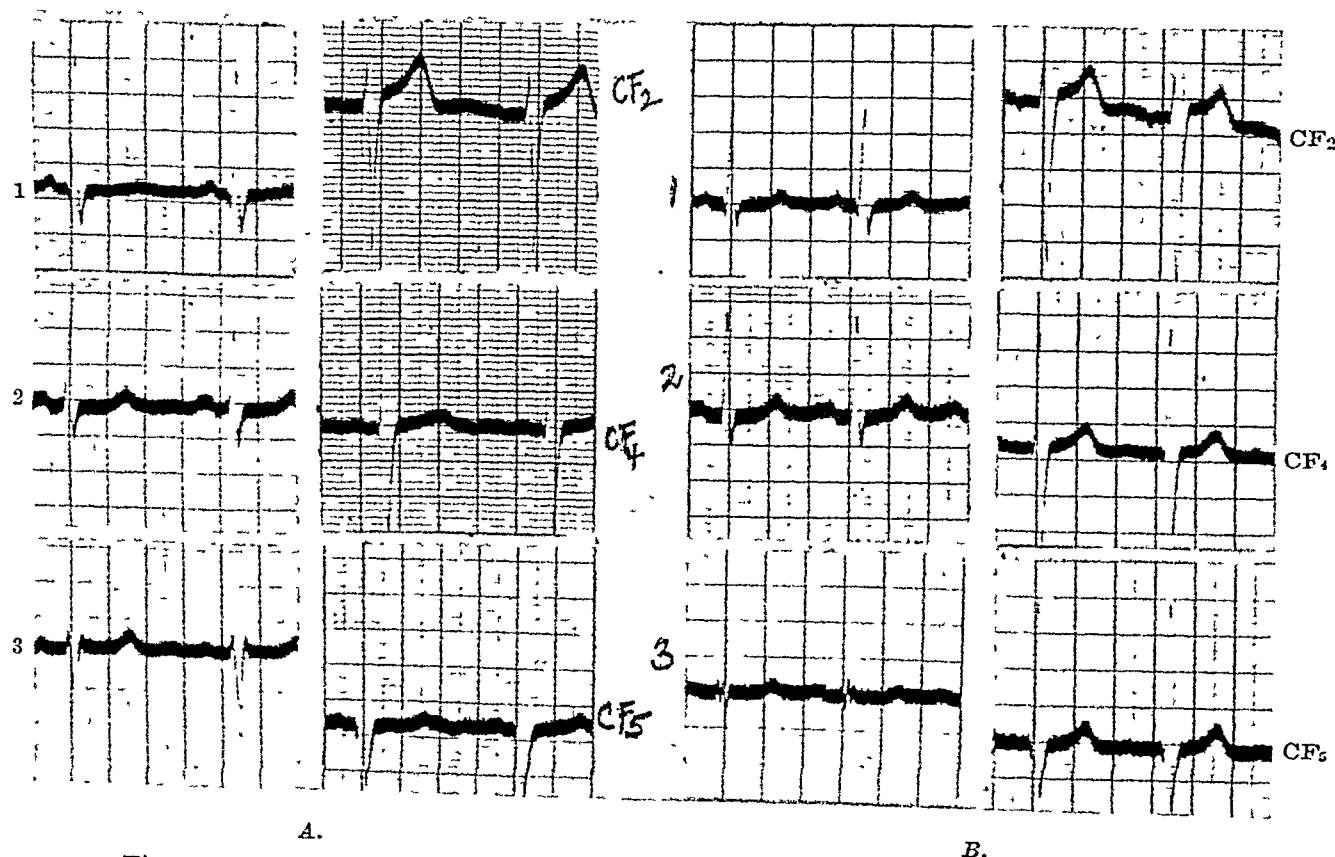


Fig. 12.—E. V. H., a man, aged 44 years. A, Electrocardiogram taken Aug. 2, 1944; blood pressure, 210/130. B, Taken Aug. 30, 1944; blood pressure, 160/105. Sympathectomy Aug. 8 and 18, 1944.

the pressure had increased, with a high point of 250/165. There had been two brief episodes (lasting a few days) of numbness and tingling of the right arm and leg, disturbance of speech, blurring of vision, and difficulty in locomotion, which cleared without any sequelae. His headaches continued. He had stopped work in January, 1944. His past history was uneventful except for bilateral renal stones dating back sixteen years. There had been no cardiac symptoms.

On admission, his physical examination showed no important abnormalities except for a blood pressure of 210/130. The ophthalmoscopic examination showed Grade 2 hypertensive fundi. X-ray examination showed heart size and aortic shadow within the normal range, and small bilateral renal calculi. The electrocardiogram (Fig. 12, *A*) on August 2 showed normal rhythm (rate 70), slight to moderate left axis deviation, very low T waves in Lead I, and high R waves and very low T waves in Leads CF_1 and CF_2 . The blood was normal. The urine showed a constant slight albuminuria with highest specific gravity (concentration test) at 1.015, occasional hyaline casts, and a few red and white blood cells. Renal function (phenolsulfonphthalein) test showed readings of 20 and 43 per cent in one hour. The blood nonprotein nitrogen was 24 mg. per cent.

Bilateral lumbodorsal sympathectomy was carried out on August 8 and 18. There were no complications. He was discharged from the hospital September 6. The blood pressure on September 5 measured 165/110. The electrocardiogram (Fig. 12, *B*) on August 30, twelve days after the second stage of the sympathectomy, when his blood pressure was 160/105, showed normal rhythm (rate 90), with normal axis and normal T waves in all six leads (I, II, III, CF_2 , CF_4 , and CF_6)—an improvement over the preoperative record.

DISCUSSION

This study was made not only to determine what alterations occurred in the electrocardiogram after adequate splanchnic resection but to correlate these alterations with other changes occurring in hypertension before and after operation so that the electrocardiogram could be utilized as an aid in the prediction of results to be obtained from surgery.

As previously stated, improvement in the electrocardiogram following various operations for hypertension has been mentioned several times.¹⁻⁵ Peet and co-workers⁴ were the only ones to give any statistical data. They found the electrocardiogram to be improved in 53 per cent of 127 patients. Barnes¹ showed serial postoperative tracings of a patient who made an excellent recovery. None of the observers gave criteria for improvement, and none made any correlations. We believed that criteria should be set up upon which future comparisons could be made and by which minor changes, such as those associated with unimportant variations in heart rate,⁷ occurring in any electrocardiogram could be eliminated. That we utilized minimal criteria on only five occasions should be emphasized. The preoperative and postoperative tracings were always taken in the same positions, since changes in position have been shown to affect the form of the electrocardiogram.¹⁰

Criticism could be made that our statistics are based only on patients upon whom postoperative electrocardiograms were taken and that patients who died during the same period should have been included to give a truer picture. So far as we were able to ascertain, only thirteen of the 209 patients selected for study of the limb leads had died when this report was made. Assuming that the same mortality rate obtained in the group upon whom follow-up electrocardiograms were taken, our statistics would have been affected adversely by only 5.4 per cent. It is true, of course, that a number of the graphs included in the tables presented contain too few individuals to be statistically significant, but it is of some interest to present them as we have found them for comparison with future data when many more cases are available for analysis.

Concerning correlations made with the postoperative electrocardiogram, there are several points of interest. The fact that chances for improvement in the electrocardiogram increased as the preoperative eye-ground picture became

worse is important since the prognosis in medically treated series becomes worse as eye-ground changes become more marked.¹¹ One would expect the electrocardiogram to be worse in patients with the more striking renal changes; therefore, the lack of such correlation in our cases is of significance. The absence of definite positive correlation between the postoperative electrocardiogram and the preoperative heart size, the patient's age, and the known duration of hypertension can be partially accounted for by the lack of definite positive correlation between these and the electrocardiogram before operation.³ It is important, however, that chances for improvement in the electrocardiogram were not decreased in those with enlarged hearts, in those with a long-standing history of hypertension, or in those in the upper age brackets.

It is difficult to obtain a reliable diastolic blood pressure with which comparisons may be made since there are so many variables: the general state of the patient, the attitude, the acuity of hearing of the person taking the pressure, and the position of the patient. Despite inaccuracies, we believe that definite positive and negative correlations between postoperative electrocardiographic changes and preoperative or postoperative diastolic pressures are of considerable value. The greater incidence of improvement in the electrocardiograms of the patients with higher preoperative diastolic pressures is encouraging since it is in this group that relief of strain on the heart is most important. The symptoms of chest pain and dyspnea may be misleading unless they are carefully evaluated (both may be due to causes unrelated to hypertension or myocardial or coronary insufficiency). Nevertheless, they were included in our series of correlations, as were Q and T waves, in order to determine their value in deciding the advisability of operation in a given individual. Believing that it was important that improvement have duration, changes in the electrocardiogram were correlated with the length of time after operation at which they were taken. The changes in electrocardiograms taken later than six months after sympathectomy were important from another viewpoint—they represented specific results of splanchnic resection since nonspecific effects of operation doubtless had disappeared by this time. A further report will be made in the future of follow-up studies along this line.

The follow-up study of hypertensive patients on whom precordial leads have been done has to date been too brief for adequate appraisal of the changes in them since the majority of the electrocardiograms in this group were taken less than a month after sympathectomy, since nonspecific effects of the operation cannot be ruled out, and since a follow-up study six months or a year after operation will be needed to confirm the present evidence of improvement. However, in spite of that fact and the present difficulties in obtaining a series of precordial leads which are accurately placed, the evidence that improvement does occur seems incontrovertible. In electrocardiography the only comparable reversals in the precordial T waves that are well recognized at present occur with recovery from acute pericarditis, evolution of and recovery from myocardial infarction, and improvement after coronary insufficiency. Although the evolution of the precordial leads has not yet been adequately followed up in the case of hypertensive patients who have not been subjected to lumbodorsal sympathectomy for us to state definitely that such striking changes do not ever occur in them, no such improvement has been noted in those on whom we have obtained serial records to date. A careful long-term study of such cases is needed.

To explain these changes of the T waves toward the normal we shall probably have to know more about the physiologic effects of sympathectomy and also more about the actual mechanism of formation of the T wave itself. From this series we can conclude that definite changes toward the normal do occur

in the T waves of the precordial leads in a considerable percentage of hypertensive patients after lumbodorsal sympathectomy and that these evidences of improvement probably mean a lightening of the load (strain) on the left ventricle, a perfectly plausible effect of the reduction of the blood pressure from excessively high levels.

SUMMARY AND CONCLUSIONS

A study has been made of the effect of lumbodorsal sympathectomy (Smithwick's technique) on the electrocardiograms of hypertensive patients. Two groups of cases were used, an earlier one for the limb leads and a later group for precordial Leads CF_2 , CF_4 , and CF_6 after they began to be taken routinely in the study of the hypertensive patient. Lead IV was considered inadequate for this statistical analysis because of its inaccuracies. Although the limb leads and the multiple precordial leads were studied in two different groups, the conclusions concerning the limb leads of the cases of the earlier series were evidently applicable to the limb leads of the cases of the later series which formed the basis of the precordial lead study. It was generally, though not always, true that the changes in Lead I paralleled those in Leads CF_4 and CF_6 ; the last named was probably the most sensitive of all.

A striking improvement in the electrocardiogram, both in the limb leads and in the precordial leads, has been found in many cases of hypertension after radical lumbodorsal sympathectomy, details of which follow.

There has remained to be carried out a similar study of the evolution of the electrocardiogram in hypertension without the specific lumbodorsal splanchnic resection and a report concerning this follows in the third paper of the present series.

A. Limb-Lead Electrocardiograms.—Two hundred nine consecutive patients upon whom lumbodorsal sympathectomies were performed at the Massachusetts General Hospital were selected for study of the limb-lead electrocardiogram. Eighty-seven postoperative electrocardiograms were compared with those taken before operation on seventy-four patients whose records were abnormal to start with.

Postoperative electrocardiographic changes (changes in the T wave in Lead I, the electrical axis, and electrocardiogram as a whole) were correlated with preoperative eye-ground findings, heart size by teleroentgenogram, symptoms (dyspnea and chest pain), and the diastolic blood pressure on admission. They were also correlated with pathologic findings in renal biopsies, the length of time after operation at which the electrocardiograms were taken, and improvement in the diastolic blood pressure later than six months after splanchnic resection. Improvement in the T wave in Lead I was correlated with the degree of abnormality of the T wave before sympathectomy.

Criteria for improvement were established by which most minor nonspecific changes in the electrocardiograms were eliminated from our statistics. Improvement or unfavorable change in the T wave in Lead I or the electrical axis meant an elevation or depression of at least 1 mm. in the T wave and a shift of at least 15 degrees in the axis. Referring to the electrocardiogram as a whole, improvement meant improvement in the T wave or axis with or without changes in the other, or considerable improvement in one with only slight unfavorable change in the other. Unfavorable change in the electrocardiogram meant undesirable change using the same standards.

From these analyses and correlations, our limb-lead findings were as follows:

1. Electrocardiographic manifestations of hypertensive heart disease were frequently reversible by adequate splanchnic resection.

2. When changes occurred in the RS-T junctions and segments, the shift occurred in the same direction as that of the T waves but to a lesser degree. The RS-T junction and RS-T segment changes sometimes were insignificant and difficult to measure.

3. Improvement in the T wave of Lead I consisted of an elevation of the T wave.

4. Associated with the improvement in the height of the T wave in Lead I, the most frequent alteration in Lead III was a lowering of the T wave. Many times an upright T wave in Lead III became inverted, as it should be normally in many individuals.

5. Less frequently, improvement in Lead III consisted of elevation of the T wave. This change occurred in cases in which the T wave had been depressed by the hypertension.

6. Improvement in the T wave in Lead I was more marked than that in Lead III; therefore, when a change was measurable in Lead II, it was in the same direction but usually to a lesser degree than that in Lead I.

7. When improvement consisted of elevation of the T waves in Lead III, as well as in Lead I, the predominant change was in Lead II.

8. According to our criteria, the T wave in Lead I improved in 47.1 per cent, became worse in 8.1 per cent, and remained unchanged in 44.8 per cent. The axis improved in 29.8 per cent, became worse (more to the left) in 12.7 per cent, and remained unchanged in 57.5 per cent. The electrocardiogram as a whole improved in 57.5 per cent, became worse in 12.7 per cent, and remained unchanged in 29.8 per cent.

9. As the preoperative eye-ground findings and diastolic blood pressure readings on admission became worse, chances for improvement in the electrocardiogram increased.

10. No positive correlation could be found between postoperative electrocardiographic findings and preoperative heart size, known duration of the hypertension, symptoms (dyspnea and chest pain), or the patient's age.

11. The presence of inverted T waves in Leads I, I and II, II and III, or I, II, and III preoperatively did not alter the operative or electrocardiographic prognosis unfavorably. They appear to be in themselves indications for surgery rather than contraindications.

12. The presence of abnormal Q waves in Lead III did not alter the prognosis adversely, but it is possible that abnormal Q waves in Lead I did so.

13. Improvement in the electrocardiogram is more or less permanent—the incidence of improvement or unfavorable change varied little with the length of time following operation.

14. Improvement in the electrocardiogram was associated with improvement of the diastolic blood pressure.

15. The deeper the inversion of the T wave in Lead I before operation, the greater was the chance for postoperative improvement in the electrocardiogram.

B. Precordial Leads of the Electrocardiogram.—Comparative studies have been made of the preoperative and early postoperative precordial electrocardiograms (Leads CF₂, CF₄, and CF₅) taken on forty-eight patients who have had the Smithwick lumbodorsal sympathectomy for hypertension. In three cases electrocardiograms taken approximately one year after operation were also available for comparative study.

There were no changes in the QRS complexes or S-T segments which could be considered significant or of help in evaluating improvement in the postoperative precordial electrocardiograms, but further follow-up of this point is necessary.

The results of studies of the T-wave changes were as follows:

1. There were no changes early postoperatively in twenty-five (52.1 per cent) of the tracings of the forty-eight cases studied.

2. In nineteen cases, or 39.6 per cent, there was definite improvement in the early postoperative precordial electrocardiograms.

a. There was definite improvement in the T waves in both Leads CF_4 and CF_5 in eleven cases.

i. In five cases there was a marked change toward the normal with either one or both of the T waves which had been inverted becoming upright.

ii. In two cases the T waves were less deeply inverted.

iii. In five cases there was an increase in amplitude of low T waves of from 1 to 5 millimeters.

b. There was definite improvement in the T wave in Lead CF_5 alone in eight cases.

i. In two cases there was marked improvement, inverted T waves becoming upright and of normal voltage.

ii. In six cases there was an increase in the low T wave voltage of from 0.5 to 1.5 millimeters.

There were three cases on which follow-up tracings were available a year after operation. In the first of these cases there was no appreciable change in the precordial leads twenty-three days postoperatively, but there was definite improvement one year later. In the second case there was no significant change either in the record taken twenty-eight days postoperatively or in the one taken one year postoperatively. In the third case there was a slight progressive change for the worse twelve days and one year after operation; a tracing taken three and one-half months afterward was normal. This patient, however, had definite angina pectoris which was occurring rather frequently, and her coronary insufficiency probably accounted for the changes. In compiling our statistics only the immediate postoperative records, however, were considered.

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THE ELECTROCARDIOGRAM IN HYPERTENSION

III. ELECTROCARDIOGRAMS OF HYPERTENSIVE PATIENTS FOLLOWED FOR A LONG TIME WITHOUT SPLANCHNIC RESECTION IN COMPARISON WITH THOSE IN PATIENTS WHO HAD HAD SPLANCHNIC RESECTION

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MUCH has been written on electrocardiography in hypertension, as many papers and books can prove.¹⁻¹⁶ Modifications and abnormalities that occur in the QRS complex, as well as in the RS-T junction and RS-T segment, the T waves, and the electrical axis have been described and discussed.

But a new aspect of this interesting subject was presented before a meeting of the New England Heart Association over a year ago, by White, Smithwick, and associates.¹⁷ Two hundred nine consecutive patients, upon whom lumbodorsal sympathectomies were performed at the Massachusetts General Hospital, were selected for study by these authors; eighty-seven postoperative limb lead electrocardiograms were compared with the seventy-four records taken before operation on seventy-four patients, and forty-eight precordial electrocardiograms on as many patients were compared before and after operation.

They studied, in particular, the changes produced in the T waves in Lead I, in the electrical axis, in multiple precordial leads, and in the electrocardiogram as a whole. From this analysis they concluded as follows: "A striking improvement in the electrocardiogram, both in the limb leads and in the precordial leads, has been found in many cases of hypertension after radical lumbodorsal sympathectomy," and "There has remained to be carried out a similar study of the evolution of the electrocardiogram in hypertension without the specific lumbodorsal splanchnic resection and a report concerning this follows in the third paper of the present series."

Having become interested in these electrocardiographic changes following splanchnic sympathectomy, we sought in vain for published reports of comparable and adequate control studies, that is, studies of the evolution of the hypertension electrocardiogram in patients without such operation. Hence, we have collected as many such data as we have as yet been able to find which were based on adequate criteria. This search has been difficult and has yielded only fifty cases.

We obtained part of our material from the private files of one of us (P. D. W.) and from the records of the Massachusetts General Hospital. We were able to complete our control group through the kindness of the Heart Station of the Boston City Hospital, and Drs. Samuel A. Levine, James P. O'Hare, and Louis Wolff, to whom we are particularly indebted because they put at our complete disposal their own files of hypertensive patients' records and electrocardiograms and those of the Hypertension and Renal Clinics of the Peter Bent Brigham Hospital and of the Beth Israel Hospital, respectively.

We shall herewith compare the spontaneous evolution of the electrocardiograms of hypertensive patients with the changes already observed and pointed

out on the electrocardiograms of patients upon whom Dr. Reginald H. Smithwick performed lumbodorsal splanchnic resection, using the same criteria presented by White, Smithwick, Mathews, and Evans.

At the very beginning, our criteria for selection of the control group of hypertensive patients were:

1. Age: under 50 years when first seen.
2. Duration of follow-up: at least five years.
3. No other kind of heart disease present at the start or later.
4. At least three electrocardiograms.

Because these conditions were difficult to meet, we were forced to modify them a little. We stretched the age limit to 54 years (for six cases only) and selected some cases who had had only two electrocardiograms instead of three but who had had tracings taken over a period of five years or more. We went through several hundreds of records in order to get these final fifty cases, and we carefully reviewed their corresponding records and electrocardiograms (240 tracings). In some of the cases the routine precordial Lead IVF was included in the follow-up study, but in none were multiple precordial leads obtainable for comparison since such leads have only recently been introduced for routine use.

Our control series was composed of thirty-four women and sixteen men.

The average age of the patients when first seen was 41 years and 8 months, and the average duration of follow-up was eight years and four months (range: five to twenty-one years). If we take into consideration this last figure, it becomes easy to see why we were unable to include in our series several cases with very high and long-standing blood pressure levels or with malignant hypertension. We know how quickly, at times, the evolution of such cases leads to death.

Following the new criteria for the selection of cases, we divided our patients into two groups according to their age:

Group 1: Patients less than 50 years of age.

Group 2: Patients more than 50 years of age.

The first group was, by far, larger than the second and consisted of forty-four cases out of the total of fifty; twenty-nine were females and fifteen were males. Five females and one male were included in the second group.

TABLE I

GROUP	TOTAL	FEMALES	MALES
1	44	29	15
2	6	5	1
	50	34	16

TABLE II. "SPONTANEOUS" EVOLUTION OF THE ELECTROCARDIOGRAM IN HYPERTENSION

	CASES	%
Questionable to slight improvement	5	10
Unchanged	20	40
Worse	25	50

TABLE III. GROUP 1; PATIENTS UNDER 50 YEARS OF AGE

	NUMBER OF CASES	IMPROVED	UNCHANGED	WORSE
Females	29	5	14	10
Males	15	-	6	9
	44	5	20	19

After a careful study of these fifty cases we arrived at findings expressed in Tables II and III.

Table III shows that the five improved cases were females. We found that the improvement was slight, at the most, in three instances and only questionable in the other two. Let us present these five cases in brief and see which have shown improvement in the electrocardiogram.

CASE 1.—M. E. was 34 years of age at onset of follow-up study. Duration of follow-up was twenty-one years. Seven electrocardiograms were taken during the period of observation. The first tracing showed T_1 to be positive (+1.5 mm.) and the S-T segments isoelectric; the blood pressure at that time measured 172/98. In the last electrocardiogram T_1 was positive but higher (+3 mm.) than in the first record. The S-T segment remained isoelectric, and the axis was unchanged (+50 degrees). No electrocardiographic changes were detectable in the other five tracings. The heart size remained within normal limits during the first ten years. The eye grounds were normal at the first two examinations; there was only a very mild vascular sclerosis at the time of the last ophthalmoscopic examination. The patient was always essentially asymptomatic.

CASE 2.—M. G., 41 years of age, was followed for five years. The first tracing showed depression of the S-T segments in Lead I (+1.5 mm.), inversion of the T waves in Leads I (-3 mm.) and II, and elevated S-T segments in Lead III, with an axis angle of -11 degrees. The blood pressure measurement was 225/140. A second electrocardiogram taken five years later showed that the S-T segments in both Leads I and II had become isoelectric, that T_1 was less negative (-1 mm.), and that T_2 was now positive. The electrical axis had shifted, however, more to the left (-22 degrees). The patient was never under digitalis therapy.

CASE 3.—A. J., 48 years of age. Duration of follow-up was eight years. Six electrocardiograms were taken. In the first of them, the T waves in Lead I were positive (2 mm.). The blood pressure readings were 180/100. In the last tracing T_1 had become higher (3 mm.) and the electrical axis had shifted from +25 to +59 degrees; the blood pressure at that time was 210/110. The heart showed the typical picture of left ventricular enlargement on fluoroscopy.

CASE 4.—G. McN., 49 years of age, was observed for five years. There was a questionable improvement of the electrocardiogram in this case. In the first tracing the S-T segments in Lead I were slightly depressed but became isoelectric later. The electrical axis remained unchanged, and the blood pressure readings were always around 175/110.

CASE 5.—A. B., 42 years of age, was followed for nineteen years. There was a question of slight improvement in this case. Three electrocardiograms were taken. The S-T segments in Lead I, at first depressed, became isoelectric and T_1 appeared to be more inverted in the first and second tracings than in the last. The electrical axis became more negative (from -36 to -58 degrees). The blood pressure rose from 160/110 to 210/120.

Of the remaining thirty-nine cases in this group, the electrocardiogram was unchanged in twenty and became worse in nineteen.

TABLE IV. GROUP 2; PATIENTS AGED 50 TO 54 YEARS

	NUMBER OF CASES	IMPROVED	UNCHANGED	WORSE
Females	5	-	3	2
Males	1	-	-	1
Total	6	-	3	3

A striking point in the entire series (both groups) was the lack of improvement.

DISCUSSION

The percentage of hypertensive cases showing any improvements at all in the present electrocardiographic study during a period of several years is decidedly low. We should add that this improvement is but slight or even but questionable, at times, as can be seen from the analysis of the five cases in which any possible change for the better was found.

Our study revealed the fact that the spontaneous evolution of the electrocardiograms of hypertensive patients is unfavorable in 50 per cent of the cases followed for some years, with no change in 40 per cent more. It would seem probable that a longer follow-up would show still more deterioration.

This shift from normal to more or less abnormal tracings depends in part on the length of time elapsed since hypertension appeared but chiefly on the levels reached by the blood pressure. In other words, the electrocardiogram has more chance of getting worse and worse when the blood pressure readings become higher and higher (especially the diastolic) as time goes on.

We have been told by others of the spontaneous improvement of the electrocardiogram in occasional cases, but from our recent experience we suspect that such instances are decidedly unusual or are to be ascribed to a complication, in particular, recovery from coronary insufficiency.

The age of the patient seems also to influence, in part at least, the ulterior course of the electrocardiogram. The older the patient the more chance for his serial tracings to become worse with the progression of time and with a long-standing hypertension. The younger patients are likely to stand high blood pressure better than do the aged. This is not always true, however, because some cases do show, in a relatively early stage of hypertension, strikingly unfavorable changes although the blood pressure is not alarmingly high, in contradistinction to other cases which stand a very marked rise of blood pressure for a long period without any appreciable electrocardiographic change. Let us now present in brief a case which illustrates this resistance.

CASE 6.—J. W., 24 years of age, sought medical advice because of headaches and pain in the back of her neck of six months' duration. At that time the heart was not enlarged by clinical examination, but fluoroscopy showed a moderate prominence of the left ventricle and a marked tortuosity of the aorta. A faint apical systolic murmur was present, and the aortic second sound was accentuated and louder than the pulmonary second sound. The blood pressure was 190/150. The eye-ground examination showed the arteries to be moderately narrowed in caliber and pale in color; a slight degree of a-v nicking was also present. The electrocardiogram was quite normal (T_1 upright and 3 mm. high, T_2 slightly inverted, S-T segments isoelectric, axis angle 42 degrees). The patient was followed for eight years. During this interval the blood pressure remained always high, but especially the diastolic, reaching 180 on several occasions. An x-ray film taken at the time of the last examination showed the heart size to be just above normal limits, and the electrocardiogram was almost superimposable on the tracing taken eight years before (T_1 upright and +1.5 mm. high, T_2 slightly inverted, axis angle 38 degrees).

Why do some persons stand very high blood pressure for a long period (Case 1) without having any symptoms at all and without showing unfavorable electrocardiographic changes, while other persons do not? Would it be possible to explain this fact on the basis of the existence of an individual or familial factor?

Let us look at Tables III and IV and note that we failed to find any favorable electrocardiographic change in our hypertensive men. Although we recognize the difficulties in establishing an adequate comparison between such small and unlike numbers (thirty-four women and sixteen men), one has the impression that the unfavorable evolution of the electrocardiogram in hypertensive patients is more frequent in men than in women. In only six of the sixteen men studied did we fail to find unfavorable changes in the tracings.

This comparison of the different evolutions of the electrocardiogram in hypertension in men and in women is in keeping with a concept already well accepted in cardiology, namely, that the clinical evolution and prognosis of hypertension in women seem to be definitely better than in men.

TABLE V. ELECTROCARDIOGRAMS (LIMB-LEADS)

	SERIES OF CASES SUBJECTED TO LUMBO- DORSAL SYMPATHECTOMY		PRESENT (CONTROL) SERIES	
		%		%
Improved	50	57.5	5	10
Same	26	29.8	20	40
Became worse	11	12.7	25	50
	87	100.0	50	100

And, finally, let us compare our results with those obtained by White, Smithwick, Mathews, and Evans after lumbodorsal sympathectomy.

As one can readily see, there is a striking difference between the spontaneous evolution of the electrocardiogram in hypertensive patients and the changes which develop after lumbodorsal splanchnic resection. The last word has, however, not yet been said. We must await the judgment of time.

SUMMARY AND CONCLUSIONS

1. We have compared the electrocardiograms of hypertensive cases followed for a long time with those of patients who have had Smithwick's lumbodorsal splanchnic resection for hypertension.

2. Our control series consisted of fifty cases, forty-four of whom were less than 50 years of age when first seen; six were a few years older (from 50 to 54 years of age). There were thirty-four women and sixteen men in this group. A total of 240 electrocardiograms belonging to the fifty cases were studied.

3. The average age of these fifty patients when first seen was 41 years and 8 months, and the average follow-up period was eight years and four months (range: five to twenty-one years). No other kind of heart disease was present either at the start or later on during the evolution of the hypertension.

4. The fifty patients were divided into two groups according to age; forty-four patients less than 50 years old comprised the first group, twenty-nine of whom were females and fifteen males. Only six patients were included in the second group and their ages varied between 50 and 54 years.

5. The electrocardiograms of only five out of the fifty cases showed any possible improvement at all, and then it was questionable or slight. The serial tracings of twenty patients (40 per cent) failed to show any appreciable modification. Those of twenty-five cases (50 per cent) had an unfavorable electrocardiographic evolution.

6. All of the improved cases were women less than 50 years of age when the follow-up study began.

7. No favorable changes were detected among the male patients, or in the group of patients older than 50 years.

8. In accord with these facts, one may conclude that the electrocardiogram in hypertension tends to become worse as time goes on and that there exists a definite parallelism between the clinical course and the electrocardiographic evolution of this disease. Age, sex, and especially the passage of time appear to act unfavorably in the evolution of the hypertensive electrocardiogram.

9. There is a striking difference between the spontaneous evolution of the hypertensive electrocardiogram and the picture which develops after lumbodorsal sympathectomy markedly in favor of the latter.

10. A longer period of time must elapse, however, before final judgment can be passed concerning sustained improvement of the hypertensive electrocardiogram after lumbodorsal sympathectomy.

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CLINICAL OBSERVATIONS WITH CERBERIN

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THIS publication is for the purpose of describing the first use of cerberin on human subjects.

Cerberin is a glycoside which has been extracted from the kernel of *Cerbera odollam*, a tree native of India, Dutch East Indies, and certain islands of the Southwestern Pacific. DeVry,¹ in 1864, was first to discover that the expressed oil of the kernels of this tree contained a substance which had a digitalis-like action. In 1893, Plugge² found that this substance would cause systolic standstill of the frog's ventricle. More recently, Chen³ became interested in *Cerbera odollam*. His intent was to isolate cerberin and other active substances which might be present in the kernels of the nuts and to conduct various pharmacologic experiments with these pure principles. He standardized the drug according to

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the method used for digitalis. After this was done, it was at his suggestion that the following clinical work was carried out.

METHODS

It was decided that the effect of cerberin could best be demonstrated in patients with auricular fibrillation. Patients were selected who had received no previous digitalis medication and who were in sufficiently good condition to make the use of diuretics unnecessary. This was not always possible.

Upon admission each patient was given complete rest in bed, with sedation of necessary, for eighteen to twenty-four hours, and in two cases as much as ten days' rest in bed was maintained before medication was begun. This was done to discount the effects of rest upon the fibrillation before cerberin was given.

The course of the patient was followed by electrocardiograms, venous pressure by the direct method,⁴ vital capacity,⁵ chest plates, and a careful check, twice daily, of the apical and radial rates. Where the condition of the patient made it possible, circulation times were done. For this the procedure was:

Four minims of ether were injected into the antecubital vein for the arm-to-lung times and 4 to 6 c.c. of 20 per cent neocalglucon were used for the arm-to-tongue test.⁷

In the first ten cases cerberin was given intravenously as we were not familiar with its rate of absorption from the intestinal tract. In the last five cases an oral preparation was used. In each instance 1 c.c. of the solution equaled 2½ cat units. Since this is the first clinical use of cerberin, we had to proceed cautiously in its administration. Therefore, in the beginning, we decided not to give more than 5 cat units per day intravenously. When the oral preparation was used, it was given in sufficient doses to slow the apex rate to the desired level and reduce the pulse deficit to a minimum.

RESULTS AND DISCUSSION

Cerberin was administered to fifteen patients, fourteen of whom had auricular fibrillation and one of whom was in congestive failure with a regular rhythm. These fifteen patients were classified as follows: Four with the diagnosis of rheumatic heart disease, two with the diagnosis of hypertensive heart disease, seven with the diagnosis of arteriosclerotic heart disease, and two with the diagnosis of thyrotoxicosis.

In one case the fibrillation ceased before the effect of the drug could be determined. In two instances the fibrillation was controlled and the patients carried through surgery: one a thyroidectomy, the other a leg amputation.

The following two case histories are representative of our methods and the actions of this drug.

Mrs. O. Z., R.N. and housewife, aged 51 years, was first seen on January 14. Her complaint at that time was "blood clot in right leg."

Present Illness.—On January 4, the patient developed a severe cold. The cold gradually improved, and no cardiac complaints could be elicited. On January 12 she developed a sudden pain in the right leg followed by coldness, numbness, and loss of function of the leg. By the next day definite purplish discoloration of the foot had occurred. This progressed to involve the distal two-thirds of the right leg by the time of admission.

Past History.—Significant points in the past history were: (1) Systolic blood pressure of 180 was found at age of 21 years while she was being examined for a "strained heart." (2) In 1935 she had a mild "heart attack" and was in bed for six months. (3) She had a stroke in 1937 which resulted in paralysis of the right side of the face, right arm, and right leg and aphasia which has gradually improved since that time. No definite rheumatic history could be elicited. Family history was negative.

Physical Examination.—The patient was in a fairly good condition. She showed a mild speech defect. The ocular fundi showed tortuous arteries with notching at the arteriovenous crossings. The lung fields were clear. There was slight enlargement of the heart on physical examination. There was a rapid fibrillation with an apex rate of 165 to 170 and a radial rate of about 80. No definite signs of congestive heart failure were found. Blood pressure was 160/110.

There was a purplish discoloration of the right foot and the distal two-thirds of the right leg. The foot was cold, and no dorsalis pedis pulse was palpable.

Laboratory.—Urine and blood findings were normal. Total nonprotein nitrogen was 28 mg. per cent. Clotting time was three minutes; bleeding time, one minute. Serology was negative. Electrocardiogram showed auricular fibrillation with ventricular rate of 165 per minute.

X-Ray.—X-ray of the chest showed no definite signs of congestive failure; it showed enlargement of the heart with accentuation of left auricular curve and a suggestion of mitral stenosis.

Diagnosis.—The diagnosis was arterial hypertension and possible rheumatic heart disease with mitral involvement, auricular fibrillation, and embolus in right popliteal artery with early gangrene of right leg.

Course and Treatment.—The patient was kept at rest in bed, and given mild sedation with phenobarbital and codeine. The fibrillation was controlled with cerberin. Venous pressure on admission was 8.5 cm. of water. Fifteen days later it was 7.5 cm. of water. Arm-to-lung time on admission was 8.2 seconds; fifteen days later it was 7.5 seconds. Arm-to-tongue time on admission was 22 seconds; fifteen days later it was 15 seconds. Vital capacity improved from 38 per cent at admission to 64 per cent at discharge. Electrocardiograms showed a gradual slowing of the ventricular rate from 165 per minute to 80 per minute.

Amputation of the right leg to 20 cm. above the knee joint was done on the seventh day of the patient's hospital stay with an uneventful recovery.

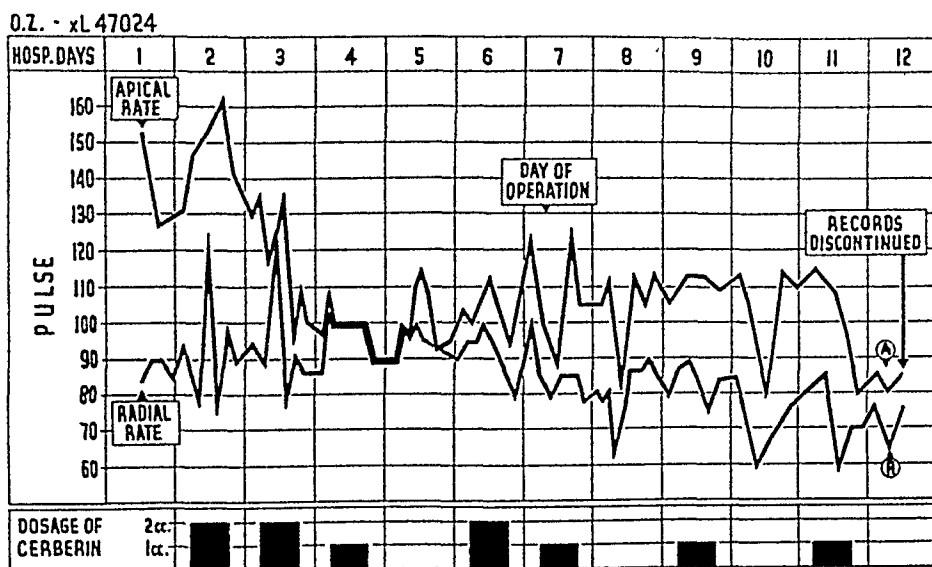


Fig. 1.

Fig. 1 shows the record of the apical and radial rates and the dosage of cerberin given. Fig. 2 shows the electrocardiogram on admission and after five days on the preparation.

CASE 2.—E. S., a white woman, aged 75 years. Her chief complaints were "heart fluttering" diabetes, and a cold right foot.

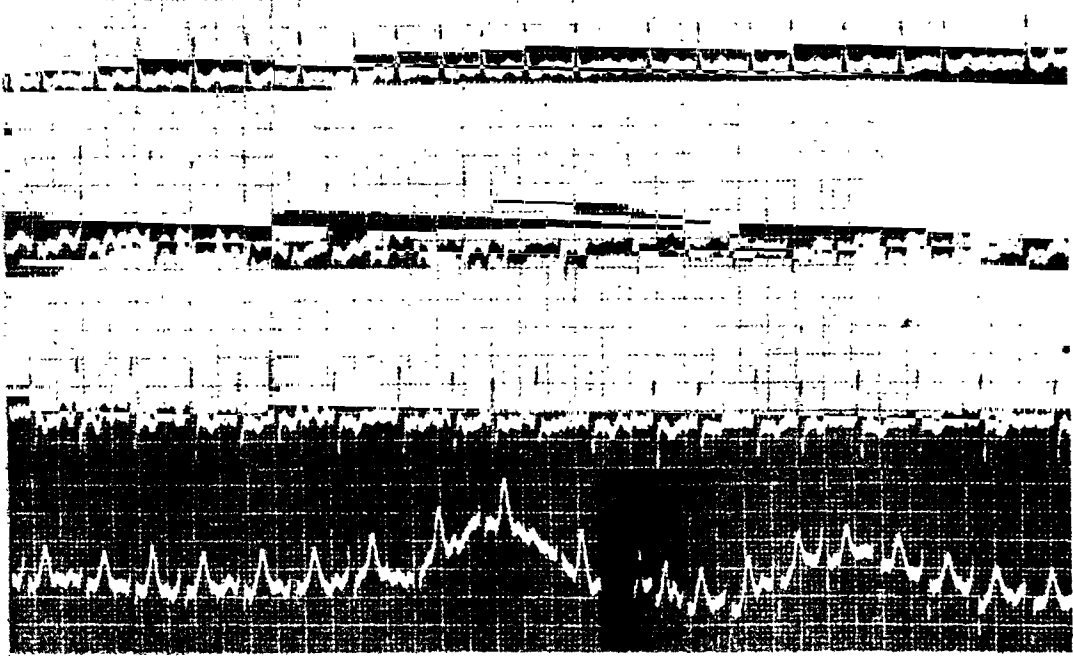
Present Illness.—Her ability to exercise had been greatly limited for the previous two to three years because of shortness of breath accompanied by irregularity of the heart. She had had mild swelling of the feet and ankles for the same period of time. Two weeks before admission she developed a sudden pain in the right foot which had since become blue and cold. She was known to have diabetes for the previous three years.

Physical Examination.—Positive findings: Eyes, moderate arteriovenous nicking with tortuosity of the arteries; slight orthopnea with overdistention of the jugular veins in the flat posture; lung fields, clear; heart, auricular fibrillation present, apex in fifth intercostal space about 1 cm. to the left of mid-clavicular line, blowing Grade 2 systolic murmur at mitral area; liver, not palpable; extremities, no edema, right foot blue and cold up to 3 inches above lateral malleolus, no arterial pulsation in this foot, but present in the left; walls of radial arteries felt thickened upon palpation.

Laboratory.—Urinalysis: heavy trace of albumin; 2 to 3 per cent sugar; 8 to 10 pus cells. Blood: hemoglobin, 13; white blood cells, 6,800 with normal differential. Blood sugar, 168 mg. per cent. Phenolsulfonphthalein test, 72 per cent in fifteen minutes.

DATE	TIME	VENOUS PRESSURE	ETHER	CIRCULATION TIME (SEC.)		ECG
				CALCIUM GLUCONATE		
6/12/42	11:30 A.M.	15.5 to 16.0 cm. H ₂ O	18	39 to 32		+
6/17/42	5:00 P.M.					+
6/18/42	2:00 P.M.	8.5 to 9.0 cm. H ₂ O	10.0 to 5.0	23.5 to 11.0		
6/20/42	10:15 A.M.	8.0 cm. H ₂ O		22.0		

O.Z. - xL 47024, /-15-4/



O.Z. - xL 47024, /-20-4/

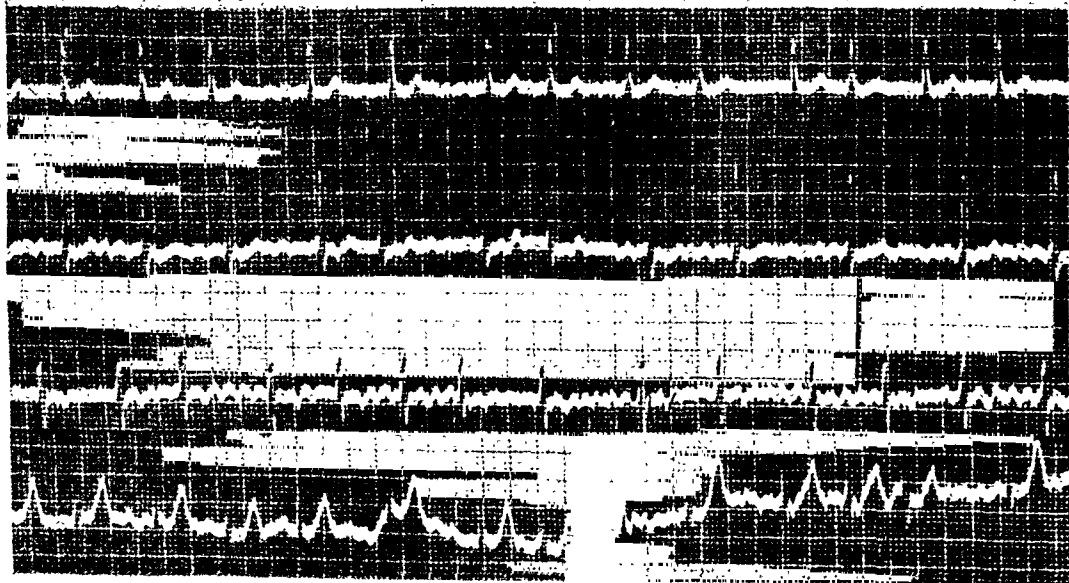


Fig. 2.

X-Ray.—X-ray showed definite cardiac enlargement.

Treatment.—The treatment consisted of rest in bed, sedatives, and cerberin.

Fig. 3 shows the record of apical and radial rates and dosage of cerberin. Fig. 4 shows the electrocardiogram on admission and after five days on the drug.

DISCUSSION AND RESULTS

Of the fifteen people who have received treatment with cerberin, in two instances it was found that no medication was necessary, and so the drug was discontinued. One patient was moribund on admission and died soon afterwards. In one patient with congestive failure and a regular heart rate no benefit was obtained from the use of cerberin. In this instance the drug was discontinued, the patient was digitalized, and mercurial diuretics were used. However, none of these measures resulted in complete compensation of the patient.

Of the remaining eleven patients, two had auricular fibrillation with no evidence of congestive failure. The remaining nine had auricular fibrillation and were in congestive failure, as confirmed by both clinical and laboratory findings. In six of these patients cardiac compensation resulted after the fibrillation had been controlled with cerberin and the patient kept at rest in bed with sedation. In three instances these measures were ineffectual, and diuretics were necessary in order to bring about compensation.

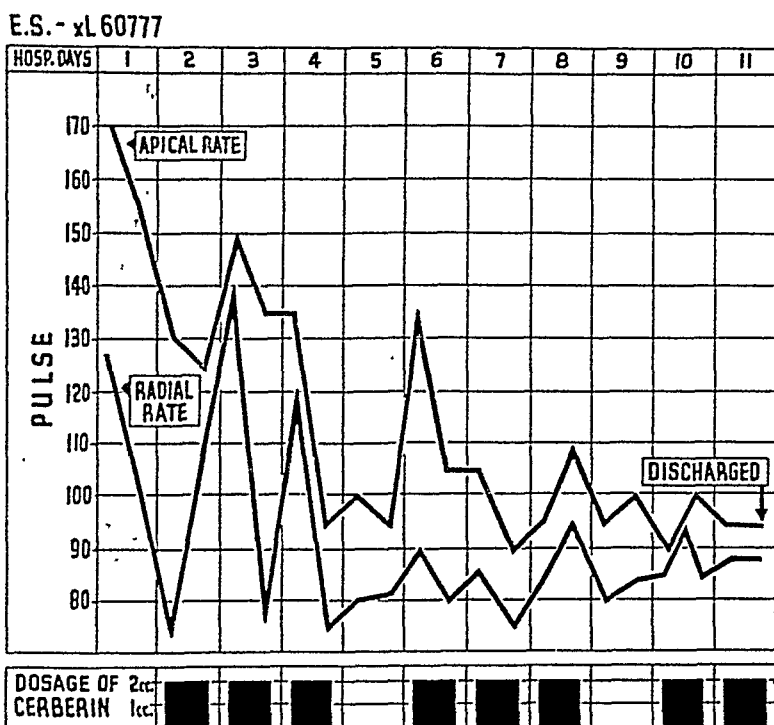


Fig. 3.

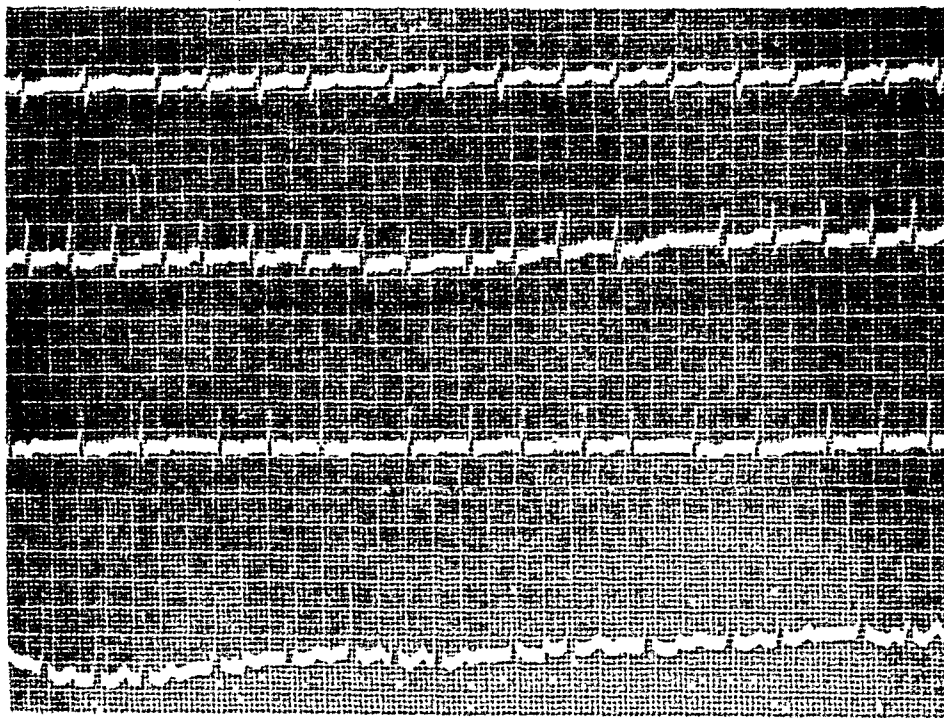
We do not intend to intimate that the control of fibrillation alone resulted in compensation in these cases. We do not know the complete action of cerberin, and in this paper we are dealing only with its effect on fibrillation.

It was noted that cerberin produced a slowing of the pulse much more quickly than did digitalis. One patient demonstrated this especially well. A woman with advanced mitral stenosis, intense cyanosis, orthopnea, cold, clammy extremities, an apical rate of 160 per minute, and a radial rate too feeble to count was given 10 cat units of cerberin intravenously. Within five minutes after injection, her pulse was reduced to 110 per minute with no pulse deficit, and there was a remarkable improvement in all symptoms noted above.

On the other hand it was noted that the effect was much more transitory than with digitalis. For example, in one case which had a very rapid fibrillation and had been controlled with cerberin, discontinuance of the drug resulted in a return of the pulse to a pre-medication level in thirty-six hours.

No untoward effects were noted with administration of cerberin except in one case. In this instance the patient's apical rate had been slowed by the drug to about 50 per minute, and he developed anorexia, nausea, vomiting, and abdominal cramps. The drug was stopped, and on the third day all symptoms had disappeared.

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E.S. - xL 60777, 6-17-42

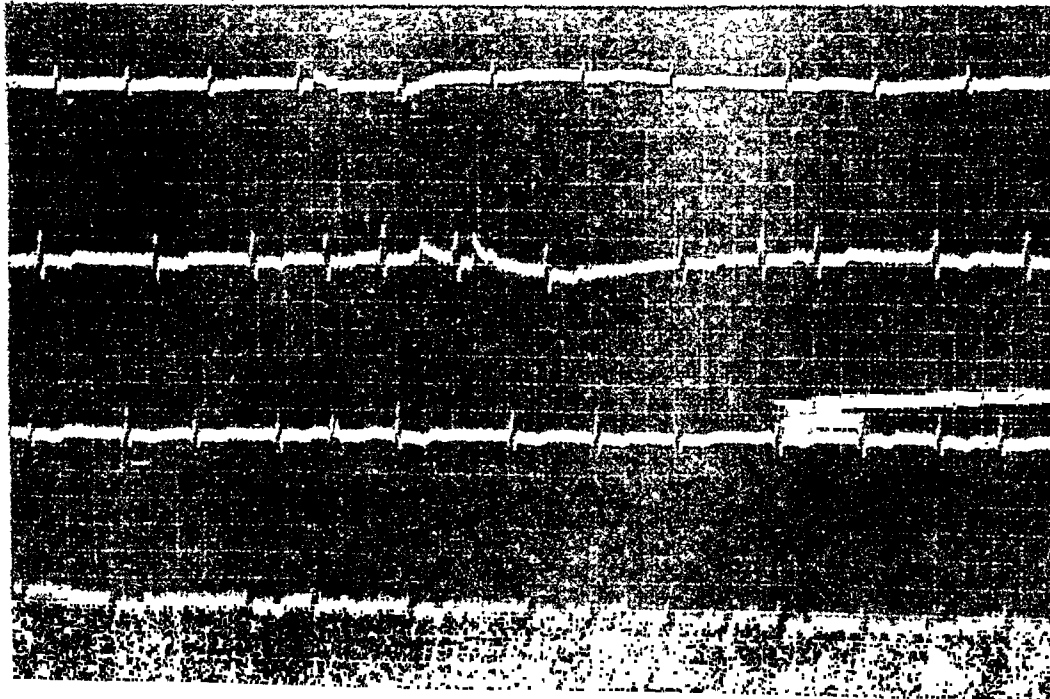


Fig. 4.

Table I is a summary of all the cases in which the drug was tried and the results obtained.

Since our series of cases is small and we had to proceed cautiously in the administration of the drug, we were not able to estimate the average dose necessary for control of auricular fibrillation.

TABLE I

NAME	AGE (YRS.)	DIAGNOSIS	DAYS ON DRUG	METHOD OF AD- MINIS- TRATION	CIRCULATION TEST (ON ADMISSION)	CIRCULATION TEST (ON DISCHARGE)	COMMENT
L. K.	93	Arteriosclerotic heart disease with auricular fibrillation	28	Per os.	Unable to cooperate	Ether = 20 seconds CaGlu. = 37 seconds Ven.Pr. = 25 cm. H ₂ O	No other medication necessary Ceased fibrillating. Drug discontinued
M. M.	35	Rheumatic heart disease with auricular fibrillation	5	I.V.*	Ether = 20 seconds CaGlu.† = 53 seconds Ven.Pr.‡ = 26 cm. H ₂ O	Ether = 7 seconds CaGlu. = 17 seconds Ven.Pr. = 12.6 cm. H ₂ O	No other medication necessary
E. M.	58	Rheumatic heart disease. Auricular fibrillation. Decompensated	18	I.V.	Ether = 10 seconds CaGlu. = 22 seconds Ven.Pr. = 18.6 cm. H ₂ O	Ven.Pr. = 24 cm. H ₂ O Vit.Cap.§ = 39%	Diuretics necessary to compensate
N. P.	43	Rheumatic heart disease with auricular fibrillation. Slightly decompensated	40	Per os and I.V.	Ven.Pr. = 41 cm. H ₂ O Vit.Cap.§ = 33%	Ether = 7.5 seconds CaGlu. = 15 seconds Ven.Pr. = 7 cm. H ₂ O	No other medication necessary. Leg amputation
O. Z.	51	Hypertensive heart disease with auricular fibrillation. Slightly decompensated	10	I.V.	Ether = 8.2 seconds CaGlu. = 22 seconds Ven.Pr. = 8 cm. H ₂ O	Ether = 5 seconds CaGlu. = 12 seconds Vit.Cap. = 73%	Diuretics unnecessary
C. M.	50	Hypertensive heart disease with auricular fibrillation. Decompensated	17	IV.	Ether = 9.6 seconds CaGlu. = 25 seconds Vit.Cap. = 41%	Ven.Pr. = 12 cm. H ₂ O Ven.Pr. = 11 cm. H ₂ O Vit.Cap. = 58%	No other medication necessary. Thyroidectomy necessary
M. K.	53	Thyrototoxicosis with auricular fibrillation. Decompensated	39	I.V.	Ven.Pr. = 26.5 cm. H ₂ O Ven.Pr. = 33 cm. H ₂ O Vit.Cap. = 34%		No other medication necessary. Thyroidectomy necessary
C. S.	57	Arteriosclerotic heart disease with auricular fibrillation. Decompensated. Carcinoma of rectum	41	Per os	Excellent results Records lost		Diuretics necessary
E. P.	47	Hypertensive heart disease with auricular fibrillation. Decompensated	8	Per os	Ven.Pr. = 20 cm. H ₂ O	Ven.Pr. = 12 cm. H ₂ O Vit.Cap. = 59%	Treatment unsatisfactory
H. D.	32	Rheumatic heart disease. Not fibrillating. Decompensated	46	I.V.	Ven.Pr. = 23 cm. H ₂ O Vit.Cap. = 35%	Ether = 9 seconds CaGlu. = 16 seconds Ven.Pr. = 12 cm. H ₂ O	No other medication necessary
C. K.	70	Arteriosclerotic heart disease with auricular fibrillation. Decompensated	13	I.V.	Ether = 15 seconds CaGlu. = 32 seconds Ven.Pr. = 16 cm. H ₂ O Vit.Cap. = 65%	Ether = 5 seconds CaGlu. = 22 seconds Ven.Pr. = 8 cm. H ₂ O	No other medication necessary
E. S.	75	Arteriosclerotic heart disease with auricular fibrillation. Decompensated		I.V.	Ether = 8 seconds CaGlu. = 35 seconds Ven.Pr. = 15 cm. H ₂ O		No medication necessary
A. H.	70	Arteriosclerotic heart disease with auricular fibrillation. Decompensated	2	I.V.	Patient unable to cooperate		No other medication necessary
A. H.	73	Arteriosclerotic heart disease with auricular fibrillation. Decompensated	39	Per os.	Ven.Pr. = 15 cm. H ₂ O		Treatment unsatisfactory. Patient died
T. W.	58	Thyrototoxicosis with auricular fibrillation. Decompensated	3	Per os	Unable to cooperate		

*I.V. = intravenously.

†Ven.Pr. = venous pressure.

‡CaGlu. = calcium gluconate.

§Vit.Cap. = vital capacity.

We were interested in determining whether or not any electrocardiographic changes occurred during medication with this drug. Since we used the drug almost entirely on patients with auricular fibrillation, we were unable to determine if the drug produced any change in the P-R interval. In three instances, definite inversion of the T waves was noted. It has been found, however, that, in cats, when cerberin was given by slow perfusion up to the fatal dose and serial electrocardiograms were taken, definite cardiographic abnormalities occurred. The first change was a definite slowing of the rate. This was followed by a prolongation of the P-R interval. Complete A-V block followed this. With increasing doses, ventricular tachycardia occurred which changed to ventricular fibrillation resulting in the death of the animals.³

SUMMARY

1. Auricular fibrillation can be controlled satisfactorily with the intravenous or oral use of cerberin.
2. Cerberin exerts its effect on auricular fibrillation much more rapidly than does digitalis. Its effect is also more transitory after the drug is discontinued.
3. No untoward effects were noted when therapeutic doses of the drug were used.

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Clinical Reports

ANGINA PECTORIS ASSOCIATED WITH DEXTROCARDIA AND SITUS INVERSUS (CASE REPORT)

LIEUTENANT COLONEL J. C. CAIN, M.C.

DEXTROCARDIA with situs inversus has long been recognized by physicians. It is known to occur in approximately one out of 35,000 physical examinations of recruits for the United States Army.¹ These individuals usually lead a normal life unless they have some obvious organic, valvular, or myocardial defects. The present case is of interest primarily because of its rarity. The symptoms of angina pectoris are typical, except that distribution of the pain is primarily substernal to the right of the sternum and down the ulnar side of the right arm. This man was inducted into the Army and performed the regular Army duties for approximately one month. He was admitted to the hospital because of an infected right toe. During his stay at the hospital it was found that he had complete transposition of all the organs of the body and symptoms typical of angina pectoris. He was discharged from the Army because of angina pectoris and dextrocardia with situs inversus.

CASE HISTORY

A 33-year-old Russian Jewish man, entered the Station Hospital, Camp Gruber, Oklahoma, Aug. 23, 1942, complaining of an infected right large toe. This infection rapidly subsided. Dextrocardia was discovered in 1924, but no symptoms were present. In 1940, while helping to carry an object weighing approximately 275 pounds, his first attack of substernal distress occurred. The pain was described as being "severe, constricting, like a pressure, and squeezing" in nature. It was located in the mid-sternal region and just to the right of the sternum. The pain lasted only a few minutes. He was very frightened and "felt sure he was going to die." He "broke out in a cold clammy sweat," and the pain radiated down the ulnar side of the right arm as far as the tip of the fourth and fifth fingers. Following this he entered the King's County Hospital, in Brooklyn, N. Y., and was told that he had dextrocardia and angina pectoris. Electrocardiograms were taken and supposedly confirmed the diagnosis. Since that time he has had approximately seven severe attacks and innumerable minor attacks. Following a severe attack he feels weak, frightened, and nauseated, but never vomits. For the following two or three days he is unable to do any work, but during this time he has no pains. The attacks are precipitated by fright, heavy lifting, exercise, emotion, intercourse, and walking into a cold wind. Attacks are more likely to occur after large meals. Prompt relief is obtained by stopping whatever he is doing and standing perfectly still or by taking 1/100 grain of nitroglycerin. The attacks never last more than five minutes.

The patient was a very excitable Jewish individual. He had done no heavy work and had lived on relief for the previous year and a half. He had frequent headaches, pyrosis, and dyspnea. He was very nervous, did not sleep well, and smoked approximately two packages of cigarettes a day. Tremor was marked. He bit his fingernails and had excessive sweating. The angina pectoris had become decidedly worse since he had been in the Army.

The family history was interesting in that his mother and three maternal uncles died suddenly from heart disease. Unfortunately, he did not know whether any of these relatives had dextrocardia. One brother was being treated for heart trouble, but the symptoms

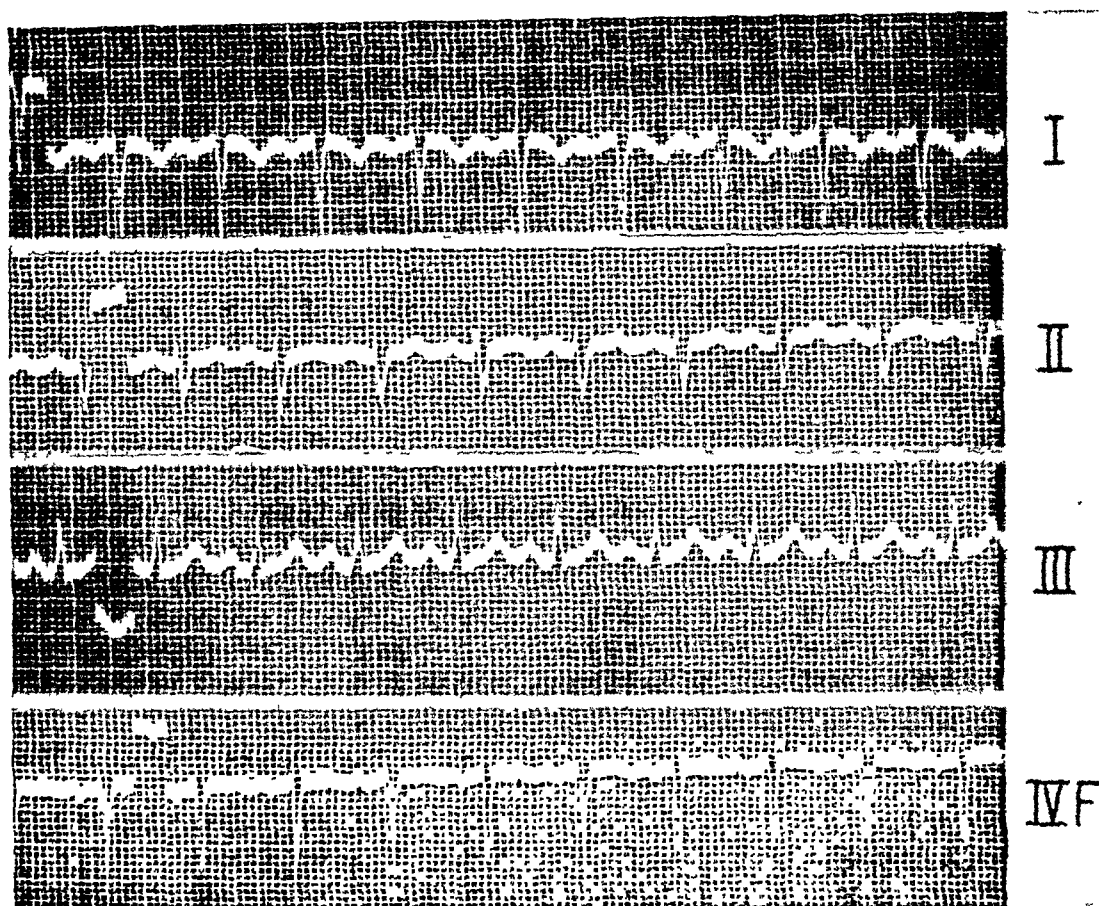


Fig. 1.—Electrocardiogram of dextrocardia showing the three standard leads and IVF. Rate 112; inversion of all complexes in Lead I, normal complexes in Lead II, and right ventricular preponderance. Lead IVF shows all complexes inverted.

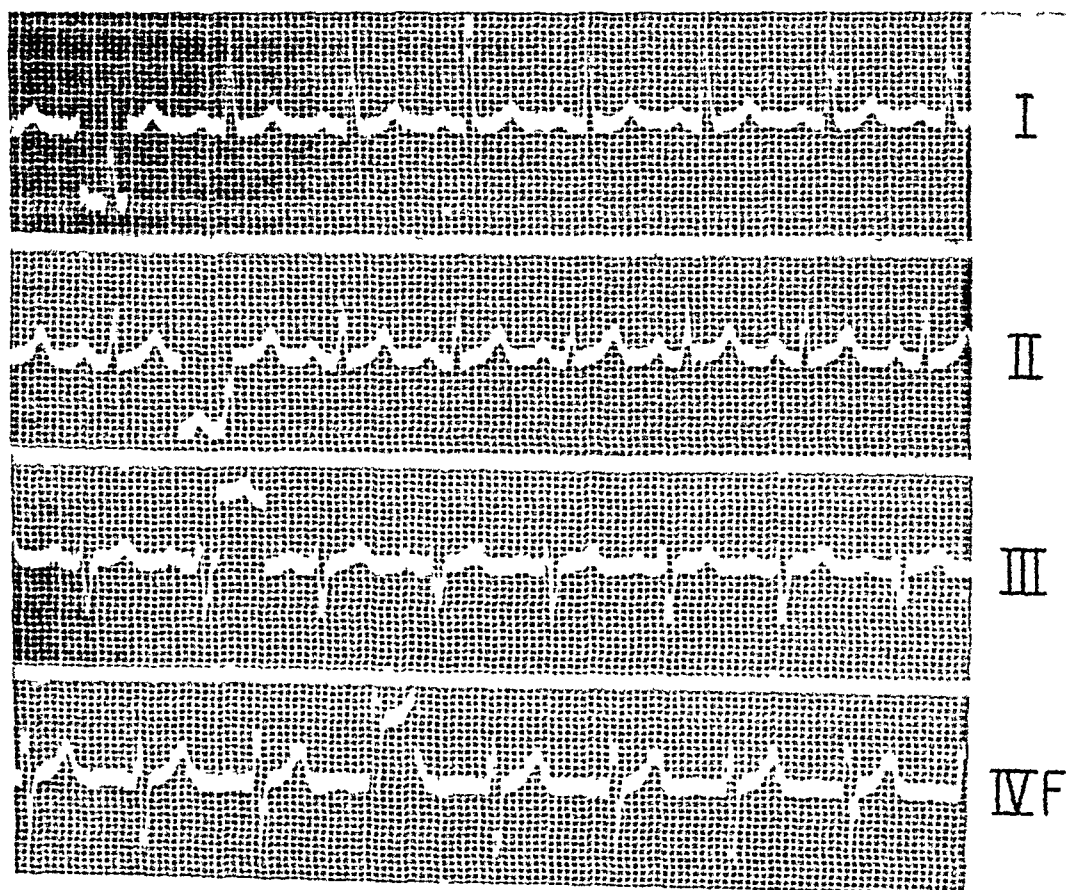


Fig. 2.—Electrocardiogram of dextrocardia after interchanging the arm wires; rate 92; all waves positive in Lead I. Lead II is the same as Lead III in Fig. 1. Lead IVF shows all complexes upright with a large S wave. This electrocardiogram shows left ventricular preponderance.

as described by the patient were highly suggestive of hysteria. The man's wife and three children were normal. The remainder of the family history was irrelevant.

The past history indicated that he had never been well or capable of participating in the usual activities of children. He had had vague joint pains, but no clear-cut history of rheumatic fever could be elicited. The only childhood disease was pertussis.

The physical examination revealed a stout, muscular individual, 5 feet, 6 inches tall, weighing 172 pounds. No gross physical defects were noted on inspection. The blood pressure was elevated, being 156/106. By percussion the heart was found to be in an unusual location with the apex located 9 cm. to the right of the mid-sternal line in the fifth intercostal space. The point of maximum intensity could easily be seen in the fifth intercostal space 9 cm. to the right of the mid-sternal line. A soft, blowing, nontransmitted systolic murmur was present in the region of the fifth intercostal space 9 cm. to the right of the mid-sternal line. The rate and rhythm of the heart were normal. Palpation of the abdomen revealed the tip of a mass in the left upper quadrant; percussion over this area suggested liver dullness. There was no evidence of a liver on the right side of the abdomen.

Roentgenographic examination of the chest and abdomen definitely showed dextrocardia and evidence of transposition of the liver, spleen, and stomach. The electrocardiogram, Fig. 1, disclosed that the rate was 112 beats per minute. All complexes in Lead I were inverted. The QRS of Lead II was downward and slurred. Lead III showed all complexes upright. By changing the arm electrodes, Fig. 2, a normal electrocardiogram, was produced. The QRS complex in Lead III was downward, and there was left ventricular preponderance. A diagnosis of dextrocardia and left ventricular preponderance was made.

COMMENT

Reports of dextrocardia associated with organic heart disease are quite rare. Willius² reported a case of dextrocardia with situs inversus complicated by hypertensive heart disease. Crawford and Warren³ recently reported the first case of coronary thrombosis in a case of dextrocardia and situs inversus, and two months later a case of hypertension and coronary heart disease associated with this condition was described by Manchester and White.⁴ It is interesting that in the case described by Crawford and Warren³ the pain associated with the coronary thrombosis was to the right of the sternum, and there was numbness of the right arm. The pain often lasted as long as an hour and frequently occurred in the absence of exercise or other recognized causes of increased cardiac work. The electrocardiogram showed clear-cut evidence of coronary thrombosis. The patient in the case described by Manchester and White⁴ complained of pain following exercise located just to the left of the sternum. There was no radiation of pain to the arms or neck.

The case described here represents the first report of typical true angina pectoris associated with dextrocardia and situs inversus. It is interesting primarily because of the radiation of the pain to the right of the sternum and down the right arm.

The exact cause of the pain of angina pectoris is unknown, but the etiology seems to be associated with coronary artery insufficiency and myocardial anoxemia. The pain fibers from the heart travel centrally over the cervical and thoracic sympathetic cardiac nerves to the white rami of the spinal nerves T₁ to T₄ and are classified as general visceral afferents. Since the heart develops as a midline structure and since it receives nerve fibers from both sides of the central nervous system, it is difficult to explain why most cases of angina pectoris have pain referred to the left side. The pain is occasionally referred bilaterally; it has been reported with reference chiefly to the right side, but the latter type is very unusual. This case seems to represent not only gross reversal of the organs but also reversal of the plan of innervation of the heart.

SUMMARY

A case of angina pectoris with pain radiating to the right arm is reported in an individual with dextrocardia with situs inversus.

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COMPLETE HEART BLOCK IN GERMAN MEASLES

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ARMY OF THE UNITED STATES

IT IS well known that auriculoventricular heart block may occur during the course of acute infections. Its frequency in rheumatic fever is generally recognized. It has been reported in such infections as diphtheria¹ influenza,² typhoid fever,³ pneumonia, scarlet fever, and typhus fever.⁴ Textbooks⁵ mention endocarditis as a rare complication of German measles, and pericarditis, myocarditis, and endocarditis as complications of measles. The occurrence of heart block in German measles has not been reported so far as we are able to determine from a review of the literature of the past twenty-six years. The rarity of this condition prompts the present report.

REPORT OF CASE

A private, aged 23 years, was admitted to the hospital on March 24, 1943, complaining of sore throat and glandular swelling in the neck which had been present for three days. The past history revealed an attack of mumps during childhood. There was no history of rheumatic fever or chorea.

Physical examination showed a moderate pharyngitis with swelling of the posterial cervical glands, most marked on the left side. The heart was of normal size. No murmurs were heard. The rhythm was regular. The blood pressure was 110/68. The examination otherwise was essentially normal.

Laboratory examination revealed 23,100 white blood cells with a normal differential count. The Wassermann and Kahn reactions of the blood were negative. Four days after admission there were 18,000 white blood cells with 78 per cent polymorphonuclear leucocytes, 15 per cent lymphocytes, and 7 per cent monocytes. During the first two weeks in the hospital the temperature ranged from 100° F. to 101° F. and then returned to normal. Five days after admission the patient was given 22 Gm. of sulfadiazine extending over a period of four days without apparent beneficial effects. On the ninth hospital day the patient became dizzy and almost fainted in the lavatory. The pulse rate was 38. An electrocardiogram taken at this time revealed complete heart block (Fig. 1). A blood count showed 11,550 white blood cells with a normal differential count. On the tenth hospital day the pulse rate was 80, and partial heart block was present with a three-to-two rhythm (Fig. 2, A). Atropine sulfate, 0.00096 Gm., was given intravenously with an immediate decrease in the

degree of block and the establishment of a one-to-one rhythm (Fig. 1, *B*). On the twelfth hospital day the P-R interval was 0.28 second (Fig. 2, *C*), and on the sixteenth hospital day it was 0.22 second. On the seventeenth and twenty-sixth hospital days (Fig. 2, *D*) the P-R interval was 0.21 and 0.16 second, respectively. On the fourteenth hospital day and five days after the onset of the complete heart block, the spleen became palpable and a generalized, pinkish, papular eruption appeared over the trunk and extremities, and to a lesser extent over the face. There were no Koplik's spots. Laboratory examination revealed

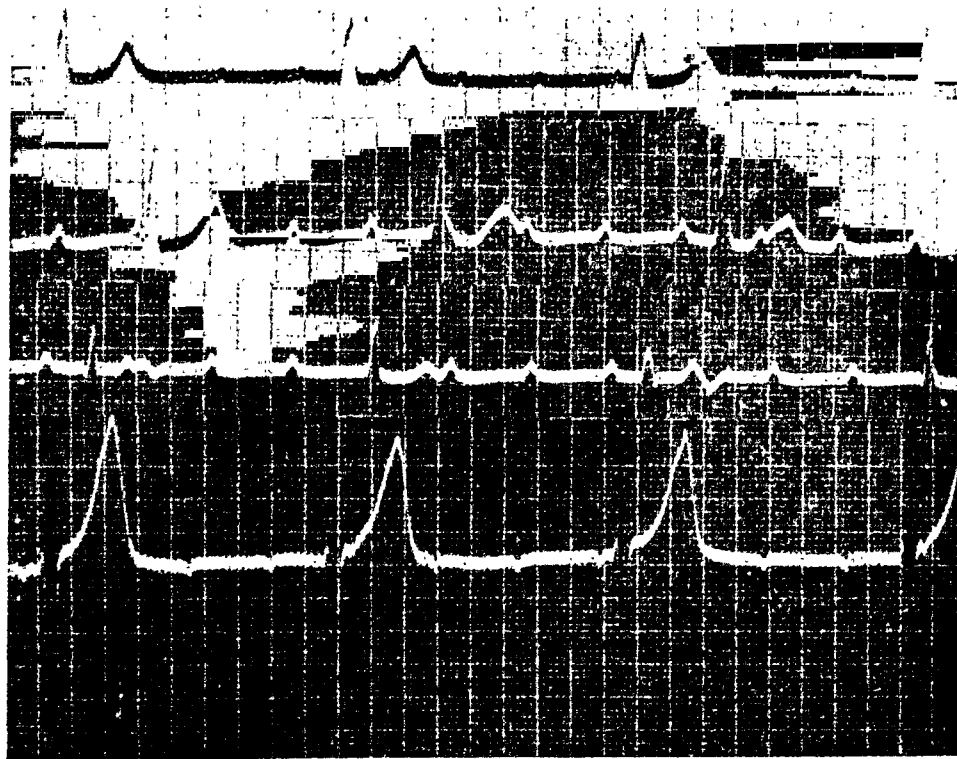


Fig. 1.

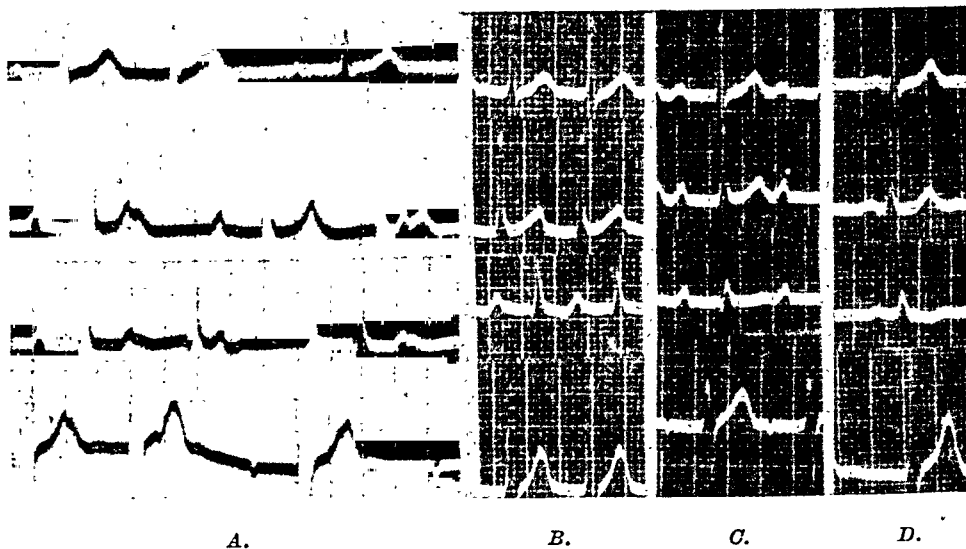


Fig. 2.

2,800 white blood cells with 52 per cent polymorphonuclears, 36 per cent lymphocytes, and 12 per cent monocytes. At no time were atypical lymphocytes seen in the blood smears. The heterophile antibody test was repeatedly positive in titer increasing from 1:28 to 1:224. Approximately one month after the appearance of the eruption it was still positive in a dilution of 1:224. The sedimentation rate was 5 mm. in one hour. Preceding the eruption the temperature reached 102.5°. Following the appearance of the eruption, the temperature

rapidly returned to normal. The glandular swelling subsided during the next few days. Convalescence was uneventful, and after a furlough the patient returned to duty on June 8, 1943.

COMMENTS

The prolonged fever, cervical adenopathy, palpable spleen, papular eruption and positive heterophile antibody test warranted the consideration of acute infectious mononucleosis. The nature and extent of the generalized skin eruption, with sudden subsidence of symptoms following its appearance, and the absence of atypical lymphocytes made this condition seem unlikely. Consultants in dermatology and in infectious diseases felt that the eruption was typical of German measles. A hematology consultant felt that the blood picture was not that of acute infectious mononucleosis. Positive heterophile tests have been reported in pneumonia, scarlet fever, measles, tuberculosis, filariasis, and aplastic anemia.⁶ The positive heterophile test in the present case was thought to be associated with the German measles.

SUMMARY

A case of complete heart block occurring during the pre-eruptive stage of German measles is reported. The heart block was of short duration, and at the end of two weeks the conduction time had returned to normal and the infection had subsided.

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Abstracts and Reviews

Selected Abstracts

Taquini, A. C., and Lozada, B.: The Ascending S-T Segment. Its Clinical Importance. *Rev. argent. de cardiol.* 11: 231, 1944.

The perusal of two thousand clinical records of patients with various diseases showed that an ascending S-T segment was present in the electrocardiogram in seventy-seven cases. The presence of this electrocardiographic pattern, most frequent in D I and D II, had no relation to the type of thorax or to the position of the heart. It was more frequent in women than in men, and the diseases most commonly associated with it were the gall bladder diseases. An ascending S-T segment was also frequently found in climacterium and in intestinal disease associated with gall bladder diseases or along with it.

AUTHORS.

Cabrera, E., and Pallares, S. D.: Determination of the Medium Manifest Axis of Unipolar Derivation of the Extremities. *Arch. Inst. Cardiol. Mex.* 14: 135, 1945.

An improvement of Sodi's formula to obtain the direction of the manifest potential axis of a given electrocardiographic deflection by means of Wilson's unipolar limb leads is described. The authors give an algebraic method to obtain this formula.

A new method of trigonometric design similar to Einthoven's original one is described, employing the values of Wilson's unipolar limb leads, instead of those of Einthoven's standard limb leads.

AUTHORS.

Pallares, S. D., Cuellar, A., and Cabrera, E.: Six Axis System With Application to the Vector AvT in Ventricular Hypertrophy. *Arch. Inst. Cardiol. Mex.* 14: 142, 1945.

A six-axis system, which was inspired by Bayley's triaxial one and includes the three-axis system of Wilson's unipolar limb leads besides those of the equilateral triangle of Einthoven is presented. The manifest axis of the T wave in ventricular hypertrophies is related to this new system and several considerations are made in regard to the changes of this wave.

AUTHORS.

Simonson, E., and Enzer, N.: An Unusual Case of A-V Nodal Rhythm With Varying A-V Block. *Brit. Heart J.* 7: 45, 1945.

A case is presented with P-R intervals varying from plus 0.22 to minus 0.19 second. The type of P waves is nodal. Episodes of gradual shortening of P-R intervals, until P follows QRS, of blocked P waves followed by Wenckebach's phenomenon, and abrupt transition from R-P to P-R intervals were observed. Two alternative interpretations are offered: (1) assumption of nodal rhythm with varying degree of at least forward, and possibly of both forward and retrograde conduction, or (2) assumption of two nodal pacemakers.

AUTHORS.

Ashman, R., Ferguson, F. P., Gremillion, A. I., and Byer, E.: The Effect of Cycle-Length Changes Upon the Form and Amplitude of the T Deflection of the Electrocardiogram. *Am. J. Physiol.* 143: 453, 1945.

In the normal heart, at ordinary heart rates, the observed T wave is mainly due to differences in the time required for repolarization of different muscle elements. Acceleration, or decrease of cycle length, reduces these differences and thus causes the associated changes which then occur in the form and amplitude of the T wave.

AUTHORS.

Simonson, E., Enzer, N., and Goodman, J. S.: Coronary Insufficiency, Revealed by Ectopic, Nodal, and Ventricular Beats in the Presence of Left Bundle Branch Block. *Am. J. M. Sc.* 209: 349, 1945.

In a case of left bundle branch block, premature ventricular beats in Leads III and CF₂ in the first electrocardiogram and nodal escape beats in Leads CF₂ and CF₄ of the second electrocardiogram, taken one day later, revealed the presence of acute coronary ventricular block in the regular beats. There was an evolution of the inverted T waves in the ectopic beats of CF₂ from the first to the second electrocardiogram. Multiple ectopic beats, due to nodal escape, in the limb leads show a shortening of the QRS intervals to normal limits and a normal QRS contour. The possible mechanism is discussed. Since the mechanism producing the ectopic beats varied, it can be concluded that the pattern of myocardial infarct or coronary insufficiency may be revealed in ectopic beats in the presence of intraventricular block, to a certain degree independent of the mechanism producing the ectopic beats.

AUTHORS.

Mehta, J. B., and Hewlett, R. F. L.: Cor Triloculare Biauriculare. *Brit. Heart J.* 7: 41, 1945.

An account has been given of the heart from a woman who lived to be 56 years of age. It was a biauricular trilocular heart, but with an imperfect auricular septum. There was a single aorta arising from the ventricle.

AUTHORS.

Robbins, S. L.: Brain Abscess Associated With Congenital Heart Disease. *Arch. Int. Med.* 75: 279, 1945.

Three cases of brain abscess associated with septal defects of the heart which came to autopsy at the Mallory Institute of Pathology of the Boston City Hospital during the years 1936 to 1943 form the body of this paper. The cases were selected from the 7,880 autopsies performed during these years, which included 53 cases of congenital heart disease of all types. There were no other instances of encephalomalacia encountered in the latter group. The total number of such cases in the literature to date is twenty-six.

In only three cases in the literature has an ante-mortem diagnosis of the disease been made and surgical drainage been instituted, a proportion which reflects principally the difficulty in diagnosis, arising in most instances from unfamiliarity with this complication of septal defects of the heart.

With the increased number of cases reported, it is to be hoped that in patients with congenital heart disease, especially in those having the tetralogy of Fallot, underlying brain abscess will be considered in the diagnosis of any focal neurological damage or meningitis. Certainly only early recognition will permit successful surgical intervention and hope for cure of this uncommon syndrome.

AUTHOR.

Taussig, H. B.: Clinical and Pathological Findings in Aortic Atresia or Marked Hypoplasia of the Aorta at Its Base. *Bull. Johns Hopkins Hosp.* 76: 75, 1945.

Aortic atresia or marked hypoplasia of the aorta at its base causes the right ventricle to pump the blood not only to the lungs but also through the ductus arteriosus to the systemic circulation. This mechanism places a great strain on the right side of the heart and is extremely inefficient for the maintenance of an adequate circulation to the body.

The outstanding clinical features produced by this malformation are intense cyanosis, great right-sided cardiac enlargement, a weak pulse in both the arms and the legs, and a low blood pressure. Fluoroscopic examination shows cardiac enlargement due to the enormous enlargement of the right ventricle; the pulmonary conus of the right ventricle and the pulmonary artery proximal to the ductus arteriosus occupy their normal position but are markedly distended. Usually there is also distention of the right auricle and the superior vena cava. The electrocardiogram shows a right axis deviation. Cardiac failure occurs early. The condition is not compatible with life for more than a few days.

AUTHOR.

Sisson, J. H., Murphy, G. E., and Newman, E. V.: Congenital Arteriovenous Aneurysms. *Bull. Johns Hopkins Hosp.* 76: 93, 1945.

A case of multiple congenital arteriovenous aneurysms in the pulmonary circulation is presented. The diagnosis established by angiography was confirmed at autopsy, and the

pathologic findings are reported. The clinical picture of six reported cases is summarized. The usual symptoms are weakness, faintness and dizziness, dyspnea, chest pain, and hemoptysis. The signs are cyanosis, clubbing of the fingers, often visible hemangiomata, bruit over chest, polycythemia, and x-ray evidence of a localized opacity in the lung. The diagnosis can be definitely established by angiography. The treatment is pneumonectomy.

A brief discussion is given of angiographic technique and the physiologic effects of pulmonary arteriovenous communications. Angiography has proved a useful procedure but may be dangerous in a patient with a circulatory shunt from right to left heart.

A clinicopathologic analysis is made of twelve previously reported cases together with the one reported of death following within one hour the intravenous injection of diodrast in diagnostic procedures. A possible conclusion one may reach from the breakdown of these data is that the intravenous use of diodrast should be approached with caution in the case of patients with hypertensive cardiorenal disease.

AUTHORS.

Holyoke, J. B.: Coronary Arteriosclerosis and Myocardial Infarction as Studied by an Injection Technic. *Arch. Path.* 39: 268, 1945.

An unselected series of seventy adult hearts were studied by the Schlesinger injection technique.

Occlusions of the coronary arteries were demonstrated in twelve of the seventy hearts. In these twelve hearts, thirty-one points of obstruction were demonstrated. Thirteen were in the main stems of the three principal coronary arteries. Eighteen were in the large branches.

Interarterial anastomoses were demonstrated in all hearts with pronounced arteriosclerotic narrowing. Only in the presence of marked hypertrophy were such anastomoses demonstrated in other hearts.

In three of eleven hearts with old occlusions of the coronary arteries there were no old infarcts. In two of five hearts with recent occlusions of the coronary arteries there were no corresponding recent infarcts.

In one of four hearts with recent infarcts there was no recent occlusion.

Grossly recognizable scars were present in the myocardium of twenty-six of the seventy hearts.

Data from this work and from the literature emphasized that coronary arteriosclerosis is only one of the many factors which may be responsible for the anatomic changes and the symptoms resulting from myocardial anoxia.

AUTHOR.

Johnson, R. S., and Lewes, D.: Advanced Mitral Stenosis at Three Years Old. *Brit. Heart J.* 7: 52, 1945.

A case of chronic (healed) rheumatic endocarditis with advanced mitral stenosis in an infant, aged 2 years and 10 months, is reported, together with the autopsy findings. AUTHORS.

Wilson, K. S., and Alexander, H. L.: The Relation of Periarthritis Nodosa to Bronchial Asthma and Other Forms of Human Hypersensitiveness. *J. Lab. & Clin. Med.* 30: 195, 1945.

In three hundred consecutive cases of periarthritis nodosa, bronchial asthma was identified in fifty-four, or 18 per cent. When differential blood counts were available, all but three of forty-seven cases of asthma (94 per cent) showed a hypereosinophilia ranging from 11 to 84 per cent, with an average of 53.5 per cent. This is in marked contrast to one hundred and fifty-one cases without asthma in which there were but nine instances of hypereosinophilia (6 per cent), and the average eosinophile count was 2.5 per cent. The association of periarthritis nodosa to the various forms of human hypersensitiveness is discussed.

AUTHORS.

Duncan, G. W.: Venous Pressure as an Index of Blood Flow in the Upper Extremity. *Arch. Surg.* 49: 235, 1944.

In the experiments described, the measurement of the rate of rise in venous pressure in the large veins of the forearm following venous occlusion is, at least to some extent, an index of the rate of blood flow in the extremity. Local application of heat to the hand and forearm and exercise of the muscles of the hand and forearm increase the rapidity of rise in venous pressure, while local application of cold decreases it.

AUTHOR.

Taquini, A. C., and Suarez, J. R. E.: *Modification of Respiration and Circulation in Arteriovenous Aneurysm*. *Medicina*, Buenos Aires 5: 109, 1945.

A report is made on five patients with arteriovenous communications; four were traumatic fistulas, three at the level of the femoral vessels, and one at the level of the deep femoral vessels. The other was a cirroid aneurysm of the leg.

The pulmonary ventilation was increased with a diminished concentration of carbon dioxide in the expired air; the carbon dioxide tension in alveolar air, the vital capacity, and residual air were within normal figures in the patients who were investigated.

The minute cardiac volume was abnormally increased in three out of five individuals, with a diminished arteriovenous oxygen difference. In three instances, the venous pressure was determined and proved normal.

The total blood volume was remarkably increased in the three patients with an increased minute volume. The globular-plasmatic relationship was normal.

These observations were repeated in three individuals after pressure by hand on the femoral artery; in two cases there was a fall in the heart rate. The minute volume was the same as prior to the compression. The venous pressure increased in all three. AUTHORS.

Herbut, P. A., and Price, A. H.: *Periarteritis Nodosa Producing Aneurysm of the Renal Artery and Hypertension*. *Arch. Path.* 39: 274, 1945.

In a case of periarteritis nodosa of the renal arteries there was an old periarteritic renal aneurysm which produced narrowing of the vascular lumen, with renal ischemia, hypertension, and death from cerebral hemorrhage following. In a second case, multiple acute periarteritic aneurysms of the intrarenal branches of both renal arteries produced hypertension, with death resulting from rupture of one of the aneurysms.

The sequence of events in the first case indicates that an aneurysm of an extrinsic portion of a renal artery can produce hypertension provided the lumen of the vessel is occluded to a degree great enough to produce renal ischemia. AUTHORS.

Katz, L. N., Wise, W., and Jochim, K.: *The Dynamics of the Isolated Heart and Heart-Lung Preparations of the Dog*. *Am. J. Physiol.* 143: 463, 1945.

Two preparations, an isolated heart and a closed circuit heart-lung, are described in which the dynamics of the circulation could be analyzed under controlled conditions. The main differences between the two preparations are (1) that in the isolated heart preparation the circuit is interrupted between the pulmonary artery and left auricle by an artificial "lung" and a pump for returning blood to a reservoir, while in the heart-lung preparation the lungs are left in situ (the artificial "lung," pump, artificial pulmonary peripheral resistance, and reservoir being omitted), (2) that artificial control is obtained in the isolated heart preparation by varying the artificial peripheral resistance placed in both the pulmonary and systemic circuits and/or the reservoir height, while in the heart-lung preparation artificial control is obtained by varying the artificial peripheral resistance placed only in the systemic circuit and/or the amount of blood in circulation.

A total of seventy-nine experiments was analyzed, 44 isolated heart, and 35 heart-lung, preparations. Graphs of various measurements were made of all these experiments using the initial control levels. These were subjected to statistical analysis in order to gain information about the circulatory dynamics in these preparations and to further knowledge of the cardiodynamics in the intact circulation. Considerations of the control of coronary flow are deferred to a later report.

In general, the experiments were of longer duration; progressive heart failure was longer, delayed, and less brusque in its development in the heart-lung than the isolated heart preparations. Among the heart-lung preparations those in which heparinized blood was used survived longer than those with defibrinated blood. The presence of progressive heart failure in some of these preparations when the initial readings were made did not affect the graphs here analyzed in any significant manner.

The significance of the various findings on the interrelation of the variables analyzed is discussed briefly.

The outstanding fact observed was the greater degree of interdependence of the various pressures and flows in the heart-lung preparation compared to the isolated heart. This is attributed to the fact that in the heart-lung preparation the main change made is in the amount of circulating blood which tends to affect all the pressures and cardiac output at the

same time and in the same direction. The greater freedom of experimental adjustment in the isolated heart nullified this to a large extent. In the intact circulation, it would appear that the changes would be interrelated somewhat as in the heart-lung preparation insofar as the adjustments are due to alterations in circulating blood volume. Change in circulating blood volume is one of the most important, but not the only, means of adjusting the dynamics of circulation in the intact animal. However, the operation of compensatory mechanisms in the intact animal, chiefly of neurogenic origin, would modify the interdependence found in the isolated heart-lung preparation.

AUTHORS.

Smith, J. R., and Henry, M. J.: Demonstration of the Coronary Arterial System With Neoprene Latex. J. Lab. & Clin. Med. 30: 466, 1945.

A method is described whereby neoprene latex is infused into the coronary vessels of the dog heart. Corrosion specimens, employing concentrated hydrochloric acid, may be made which appear to preserve all details of the coronary arterial system lumina including the capillaries. The cardiac chambers may be filled with liquid latex and the whole organ suspended by a glass hook to support the vascular casting when the myocardium is digested away. The finished specimen is kept immersed in fluid so that the minute strands are separated and details of the coronary vascular system may be seen.

AUTHORS.

Friedberg, L., and Katz, L. N.: Observations on Shock Following Bilateral Venous Occlusion of the Hind-Limbs of the Dog. Am. J. Physiol. 143: 589, 1945.

Bilateral venous occlusion of the hindlimb of the dog by means of ligation and lamp-black injection leads to a consistently fatal and rapid shocklike state. Early fluid administration (sodium chloride or plasma), demonstrated to be effective in preventing this state in unilateral venous occlusion experiments, is without beneficial action in these animals. Likewise, application of a rigid cast to both hindlimbs and lower abdomen, in order to minimize fluid leakage into the injured area, is accompanied by slightly increased length of life but does not prevent the ultimate fatal result. This suggests that some other factor, perhaps a humoral "toxic" substance plays a role. The mechanisms and possible interpretation of these results are discussed.

AUTHORS.

Zweifach, B. W., Abell, R. G., Chambers, R., and Clowes, G. H. A.: Role of the Decompensatory Reactions of Peripheral Blood Vessels in Tourniquet Shock. Surg., Gynec. & Obst. 80: 593, 1945.

The purpose of this investigation was to determine whether, in tourniquet shock, the second, decompensatory factor always appears subsequent to fluid loss or whether it may be regarded as a primary factor which normally follows, but may be independent of, fluid loss.

Experiments were performed on dogs, cats, and rabbits in which shock was produced under pentobarbital anesthesia by several different tourniquet procedures. The studies involved two methods. One consisted of continuous observations on specific physiologic reactions of the arteries, arterioles, precapillary sphincters, capillaries, collecting venules, and veins of the exteriorized omentum or mesentery. The other consisted of testing blood samples removed at intervals during the shock syndrome. The serum was injected intravenously into normal rats, and the effect on the arterioles and capillary vessels was noted in the exteriorized meso-appendix.

The initiating factor in the peripheral circulation is a reduction in rate and amount of blood flow. This occurs while the damaged limb is swelling and is associated with vasoconstriction and with hyperreactivity of the terminal vessels as observed in the mesentery and omentum.

When the syndrome is fatal two sets of contributory factors are detected: an increased viscosity of the blood, indicated by a rise in hematocrit, and the development of hyporeactivity of the terminal blood vessels. The hyporeactivity occurred while the peripheral flow was still good and resulted in pooling of blood in the capillaries and venules, thereby intensifying the reduction in the circulating blood volume. In many cases, hyporeactivity was the decisive factor in the syndrome.

Circulatory collapse in tourniquet shock is due to a reduction in blood volume caused by: (a) loss of fluid into injured limb and (b) sequestration of blood from the active circulation by pooling in the capillary bed and collecting venules. The latter is due to the development of a hyporeactive factor, which progressively interferes with the peripheral vascular compensatory mechanisms.

- AUTHORS.

Ricca, R. A., Fink, K., Katzin, L. I., and Warren, S. L.: Effect of Environmental Temperature on Experimental Traumatic Shock in Dogs. *J. Clin. Investigation* 24: 127, 1945.

In order to obtain a reproducible standardized shock experiment with the Blalock type of crusher, it is necessary to use overall pressure of 2,000 pounds for five hours on one complete upper thigh under nembutal anesthesia with the room temperature at 28° C. or above.

Any variation in these several stipulations may change the picture enough to prevent the onset of fatal shock. AUTHORS.

Ricca, R. A., Fink, K., Steadman, L. T., and Warren, S. L.: The Distribution of Body Fluids of Dogs in Traumatic Shock. *J. Clin. Investigation* 24: 140, 1945.

In traumatic shock, the fluid which extravasates into the traumatized extremity is mobilized from the rest of the tissues of the body. A portion of it is contributed by loss of circulating plasma.

The A-G ration, as determined chemically, is higher in the leg fluid from the traumatized area than that of the plasma in every case. Cell proteins apparently are liberated in the traumatized extremity, probably from ruptured muscle fibers.

The nonprotein nitrogen content of the fluid in the traumatized area is higher than that of the blood. The liberated cell proteins probably undergo breakdown into simpler nitrogenous products. The elevated blood nonprotein nitrogen during traumatic shock may, to some extent, be due to absorption of these products.

Alterations in electrolyte concentration of serum and tissues which occur during traumatic shock have been tabulated. AUTHORS.

Del Solar, A. V., Dussaillant, G. G., Brodsky, M. B., and Rodriguex, G. C.: Fatal Poisoning From Potassium Thiocyanate Used in Treatment of Hypertension. *Arch. Int. Med.* 75: 247, 1945.

Another case, the seventh thus far reported, of death due to the therapeutic use of potassium thiocyanate for hypertension is added to the literature. A distinct fault in dosage on the part of the patient was responsible for the intoxication; it emphasizes the danger of prescribing the drug in easily inaccurately measured forms, like the solution for drop administration used for this case.

The thiocyanate concentration of the blood at the onset of toxic symptoms was only 7 mg. per hundred cubic centimeters. The concentrations of the drug in the tissue are the highest ones thus far reported in similar instances. A prominent feature of the post-mortem examination was the finding of an acute necrotic nephrosis that had produced no symptoms or signs during life. AUTHORS.

Hines, L. E., and Kessler, D. L.: Venesection for the Plethoric Patient. *Arch. Int. Med.* 75: 250, 1945.

Only two of fifty-eight patients proved to have had coronary thrombosis had an erythrocyte count of less than 4,000,000. Diminished clotting time after administration of heparin and a shortened prothrombin time were the common findings for patients with high erythrocyte counts.

Similar changes in the clotting mechanism have been observed in patients known to have thrombosis. These facts suggest that the use of venesection both for preventing and for treating thrombosis is rational. The changes produced by bleeding a small number of patients seem to support the idea. AUTHORS.

Books Received

PUBLICACIONES DEL CENTRO DE INVESTIGACIONES FISIOLÓGICAS. Director: Professor Roque A. Izzo. Pabellón "Las Provincias," Buenos Aires, 1944, vol. VIII.

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Original Communications

THE EFFECT OF THEOPHYLLIN WITH ETHYLENEDIAMINE (AMINOPHYLLINE) AND OF PAPAVERINE HYDROCHLORIDE ON EXPERIMENTAL MYOCARDIAL INFARCTION IN THE DOG

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WITH THE ASSISTANCE OF GERTRUDE MOKOTOFF, A.B., AND HILLIER L. BAKER, JR.

AMINOPHYLLINE has been widely used in coronary disease as a coronary dilator because this effect has been demonstrated in the experimental animal. However, the evidence in regard to its clinical efficacy has been conflicting. Boyer,¹ in a critical review of therapeutic claims for aminophylline and related xanthine derivatives concludes that the evidence pro and con is still inconclusive.

Papaverine has been found to be a powerful and long-lasting coronary vasodilator,² much more effective than aminophylline. Clinically, we have found that it has a beneficial effect in angina pectoris,³ and this clinical impression has been confirmed by others.

Both aminophylline and papaverine have been used during acute myocardial infarction not only to alleviate pain, but with the hope that the infarct healing would be accelerated and the infarct minimized.

The evidence supporting this use of the drugs is controversial in the case of aminophylline as far as experimental myocardial infarction is concerned, and no data on the effect of papaverine in experimental myocardial infarction have been obtained. In the case of aminophylline, Gold, Travell, and Modell,⁴ working with cats, found that when therapeutic doses (about one and one-half times those recommended in man) are given intramuscularly for three weeks after ligation of the circumflex branch of the left coronary artery, the size of the infarct is not reduced, as was revealed by comparison with untreated controls. However, Fowler, Hurevitz, and Smith⁵ concluded that the infarct size in dogs following ligation of the left anterior descending coronary artery is reduced, compared with that in untreated animals, in animals treated for three weeks with aminophylline (0.2 Gm. daily by mouth, a dosage roughly equivalent to that used in man).

The present study was undertaken because of the absence of data on papaverine and the controversy concerning the efficacy of aminophylline on myo-

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cardial infarct size. The influence of these two drugs was compared by measuring the size of the myocardial infarcts eight weeks after ligation of the left anterior descending coronary artery in untreated dogs and dogs treated during this period with either aminophylline or papaverine.

It has been shown by Gregg, Thornton, and Mautz,⁶ in chronic coronary occlusion experiments, that over the course of days to weeks the retrograde flow of blood in the occluded artery increases and tends eventually to approximate the pre-occlusion inflow rate. This increasing retrograde flow leads to noticeable augmentation of peripheral coronary pressure in the occluded vessel below the occlusion and to a return of contraction in the ischemic yet viable areas produced by the initial occlusion. Furthermore, it has been emphasized by Wiggers⁷ that, while in acute experiments vasodilator drugs do not influence the functional state of myocardial regions deprived of blood by ligation, this does not preclude an increase in caliber of existing anastomoses nor the formation of new collaterals by such drugs in hearts with chronically narrowed or occluded arteries. It is in some such way that any influence of aminophylline or papaverine would be anticipated. For this reason, all the hearts used in this study had a post-mortem injection of the coronary system with a multicolored, radiopaque mixture to determine the influence these two vasodilator drugs might have had on the development or enlargement of anastomotic channels. The period of eight weeks between coronary ligation and termination of the experiment was chosen as being sufficiently long to permit the demonstration of such collateral vascular development. This estimate was based on the time for completed scar tissue formation in human myocardial infarction and on the time necessary for collateral development in chronic coronary occlusion experiments. As a further control of the development of collaterals a series of normal hearts were injected in which the coronary ligation (of the left anterior descending artery at the same site as in the other experiments) was performed post mortem.

METHOD

In a series of seventy-three dogs the left anterior descending coronary artery was ligated under aseptic precautions during anesthesia (nembutal, 25 mg. per kilogram). Artificial respiration was instituted, and the chest was opened by a 6 to 10 cm. long incision in the third or fourth intercostal space about 1 cm. to the left of the sternal margin. The pericardium was incised; the artery was isolated from the vein and ligated by means of silk. A fine, curved, ocular needle was used for the purpose. The tie was usually made just below the origin of the primary branch. In a small number, the primary branch was ligated instead, and in four instances the tie was made above the site of the primary branch. These variations were necessitated by the considerable variation in branching found in the different animals. The pericardial sac was not closed. The thorax was closed in layers with cotton thread, the pneumothorax was relieved, and the animals were permitted to breathe spontaneously. The animals were then allowed to recover from the anesthesia.

The animals were divided at random into three groups: (a) control, (b) aminophylline-treated,* and (c) papaverine-treated* groups. An equal number of dogs in the control and drug-treated groups were operated upon on the same day in order to insure comparable conditions. All dogs were housed and fed under similar conditions. They were kept in cages except that animals in the drug-treated groups were taken out for their daily drug injections.

Aminophylline was given in doses of 15 mg. per kilogram, the first dose intravenously immediately after ligation and the others subcutaneously twice daily for seven days and thereafter once daily for the remaining forty-nine days of the total eight-week course of treatment. Papaverine was administered in like manner except that the dose was 5 mg. per kilogram. The drugs were given as a 12 per cent aminophylline and 3.2 per cent papaverine hydrochloride solution in water.

*Aminophylline was kindly furnished by G. D. Searle and Co., Inc., through the courtesy of Dr. R. S. Kemp, and the papaverine hydrochloride by Parke, Davis and Co., through the courtesy of Dr. O. Kamm.

At the end of eight weeks the animals were sacrificed with nembutal and sodium cyanide and were autopsied. All the hearts were injected, dissected, and x-rayed* after the manner described by Schlesinger.⁸ The pressure used for injection was constant (150 to 200 mm. Hg) in the different preparations, and so were the injection and x-ray techniques (for the latter, 40 kilovolts, 30 milliamperes, 2½ seconds, a fine focal spot, anode-film distance of 30 inches, paper-film holder, and nonscreen film were used). The prints of the x-rays used for the illustrations were made under comparable conditions. The infarct was examined before and after the heart was dissected. Contact tracings of the endocardial aspects of the infarcted areas were made on a glass plate and subsequently retraced on transparent paper. The areas of these retracings were measured with a planimeter. Check readings by the same and several other observers were found to agree within 9 per cent; this accords with the finding of Gold and his co-workers.⁴ Sections for microscopic study were taken through the infarct, the transition zone, and in normal myocardium in all instances to compare the degree of healing in the three different groups.†

A group of twenty-nine normal dog hearts with post-mortem ties located at the site used in the operated dogs were injected. In fifteen, Schlesinger's lead-agar mixtures were used and in fourteen the mixture of lead carbonate-mercuric sulphide-gelatin used by Dock⁹ and by Prinzmetal et al.¹⁰ was employed. We have confirmed Schlesinger's observation that the lead-agar mixture penetrates arterioles less than 40 micra (and above 10 micra) in diameter in 30 per cent of our series. We have found that the lead-mercury-gelatin mixture which contains smaller particles penetrates vessels between 40 and 10 micra in diameter in 70 per cent of our cases. These facts were determined by measuring the size of the smallest injected vessels in microscopic sections with an ocular micrometer.

RESULTS

Of the seventy-three operated dogs, only forty-six were used in the final study. Twenty-one animals (27 per cent) were discarded because they did not survive the full eight-week postoperative period. Of these, thirteen succumbed within the first twenty-four hours after operation, an immediate operative mortality of 18 per cent. The cause of death in these latter animals was usually ventricular fibrillation or cardiac standstill during the operation. Data on these twenty-one dogs are summarized in Table I. Six other animals were rejected from the final study because of incomplete tie of the coronary artery, discovered at necropsy by vessel injection and dissection; there were no myocardial infarcts in this group.

TABLE I. DATA ON TWENTY-ONE DOGS THAT FAILED TO SURVIVE THE SET EIGHT-WEEK PERIOD AFTER LIGATION OF LEFT ANTERIOR DESCENDING CORONARY ARTERY

NUMBER OF DOGS	SURVIVAL PERIOD	CAUSE OF DEATH	REMARKS
11	Few minutes to few hours. Succumbed during operation or immediately after	Ventricular fibrillation or cardiac standstill	Three dogs were in puerperium and succumbed before coronary ligation
2	24 hours	Pulmonary edema or pneumonia	Irregularly outlined areas of myocardial hemorrhage and necrosis found
2	4 to 7 days	Empyema and sucking wound of chest	Indefinite areas of myocardial infarction about 2 to 4 cm. ² found
4	10 to 18 days	Undetermined	Post-mortem examinations not done due to rapid decomposition during summer heat
1	10 days	Pneumonia. Cardiac failure? Cerebral hemorrhage?	Large, soft, necrotic infarct found
1	15 days	Distemper?	No evidence of myocardial infarction

*The x-rays were taken by the X-ray Department through the courtesy of Dr. R. Arens.

†The slides were prepared in the Department of Pathology through the courtesy of Dr. O. Saphir.

TABLE II. DATA ON ALL ANIMALS TREATED WITH AMINOPHYLLINE OR PAPAVERINE AND THE CONTROLS, WHICH SURVIVED THE EIGHT-WEEK EXPERIMENTAL PERIOD FOLLOWING LIGATION OF LEFT ANTERIOR DESCENDING CORONARY ARTERY AND WHOSE HEARTS WERE INJECTED ACCORDING TO SCHLESINGER'S TECHNIQUE

CONTROL					AMINOPHYLLINE-TREATED					PAPAVERINE-TREATED				
DOG	HEART WT. (GM.)	INFARCT AREA (CM. ²)	104 × INFARCT AREA	TYPE OF ANAST.*	DOG	HEART WT. (GM.)	INFARCT AREA (CM. ²)	104 × INFARCT AREA	TYPE OF ANAST.*	DOG	HEART WT. (GM.)	INFARCT AREA (CM. ²)	104 × INFARCT AREA	TYPE OF ANAST.*
1	113	8.7	770	L-L	1A	123	6.2	504	con.	1P	152	5.1	336	L-L
2	112	11.8	1,054	con.	2A	114	8.2	719	unsuc.†	2P	153	9.8	641	L-L
3	222	11.4	514	unsuc.†	3A	120	9.5	792	L-L	3P	200	10.6	530	con.
4	102	11.5	1,127	L-L	4A	138	7.2	522	con.	4P	96	5.5	573	L-L
5	178	13.7	770	L-L	5A	106	6.3	594	L-L	5P	121	7.6	628	L-L
6	122	14.3	1,172	con.	6A	102	7.8	765	none	6P	100	5.7	570	L-L
7	90	11.5	1,267	L-L	7A	123	9.0	732	L-L	7P	117	5.0	427	none
8	123	7.4	602	none	8A	116	11.1	957	L-L	8P	110	5.3	482	L-L
9	93	6.1	656	none	9A	123	6.0	488	L-L	9P	120	6.4	533	L-L
10	163	9.7	595	none	10A	197	11.2	569	L-L	10P	100	6.2	620	L-L
11	198	9.2	465	L-L	11A	136	11.1	816	con.	11P	115	5.5	478	L-L
12	136	11.4	838	L-L	12A	113	7.5	664	L-L	12P	92	5.1	554	unsuc.†
13	80	13.9	1,738	L-L	13A	114	7.8	684	L-L	13P	78	6.6	846	L-L
14	132	9.0	682	L-L	14A	90	6.0	667	L-L	14P	83	4.9	590	L-L
15	144	12.0	833	L-L										
16	121	10.2	843	L-L										
17	128	11.0	859	L-L										
18	106	7.9	745	L-L										
Arithmetic mean					Arithmetic mean					Arithmetic mean				
Standard deviation					Standard deviation					Standard deviation				
					677					558				
					133.6					117.7				
Arithmetic mean of controls minus arithmetic mean of aminophylline-treated animals = 863 - 677 = 186					Arithmetic mean of controls minus arithmetic mean of papaverine-treated animals = 963 - 558 = 305					Arithmetic mean of controls minus arithmetic mean of papaverine-treated animals = 963 - 558 = 305				
Standard error of difference = 81.83					Standard error of difference = 81.83					Standard error of difference = 80.16				

1. *Infarct Size*.—Since the location of the tie was usually just below the primary branch of the left descending coronary artery, it is to be expected that in a larger heart a larger area is supplied by the occluded vessel and that therefore the infarct size varies, among other things, with the weight of the heart. This is actually shown to be true, when infarct size is plotted against heart weight although considerable scatter is seen (Fig. 1). The slope of the linear regression was 1 cm.² increase in infarct size per 4.42 gram increase in heart weight. Since the heart weight averages in the three groups of animals are not the same, the papaverine-treated animals having a somewhat smaller average heart weight, it was considered advisable to calculate the infarct size per gram of heart weight in comparing the three groups. The pertinent data on the forty-six dogs constituting the final series are summarized in Table II. The mean size of the infarcted area per gram of heart weight was found largest in the untreated animals, intermediate in the aminophylline-treated group, and smallest in the papaverine-treated group, the arithmetic means being 0.0863,

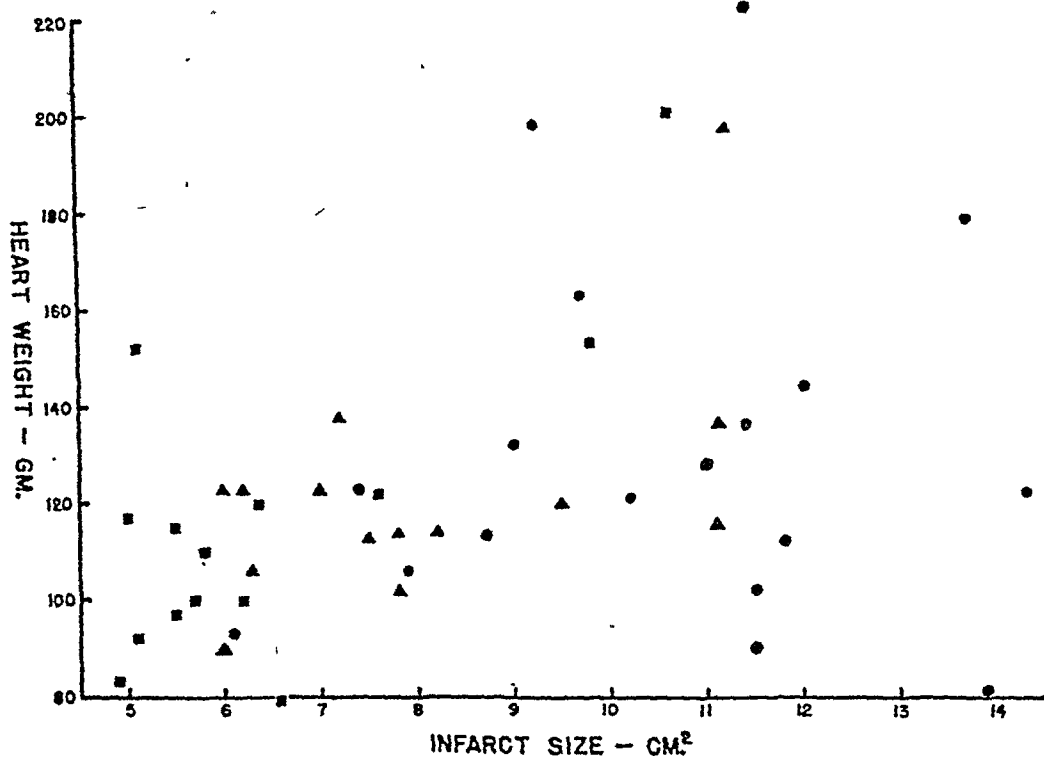


Fig. 1.—Scatter graph showing the degree correlation of infarct size to heart weight. • represents controls, □, papaverine-treated animals, and Δ, aminophylline-treated animals. Discussed in text.

0.0677, and 0.0558 cm.² per gram, respectively. The difference of the means between the papaverine-treated and the untreated animals is 0.0305 cm.² per gram, and the difference between the aminophylline-treated and the untreated animals is 0.0186 cm.² per gram. These differences were found to be statistically significant; that between the papaverine and control animals was 3.8 times its standard error, and that between aminophylline and control animals was 2.3 times its standard error. The conventional value of two times the standard error is adopted for "significance." This puts the effect of the papaverine reducing action in a high range of probability, and shows a somewhat less effective action of aminophylline with a fair degree of probability. To illustrate the drug effects graphically, the frequency distribution of the various infarct sizes per gram of heart weight in the three groups is shown in Fig. 2. In the papaverine-treated animals the maximal frequency is clearly at a smaller infarct size per gram than in the control group. In spite of some overlap, the peak frequency is also clearly different in the aminophylline-treated animals.

Obviously even greater differences were obtained when the infarct size in the three groups were compared without correcting for differences in heart size. In the papaverine-treated group the mean infarct size was 6.41 sq. cm., in the aminophylline-treated group it was 8.06 sq. cm., and in the control group it was 10.6 square centimeters.

The position of the tie did not play any significant role since the infarct size could not be related to the location of the tie with respect to the primary branching. Furthermore, the different tie locations were scattered at random among the three groups.

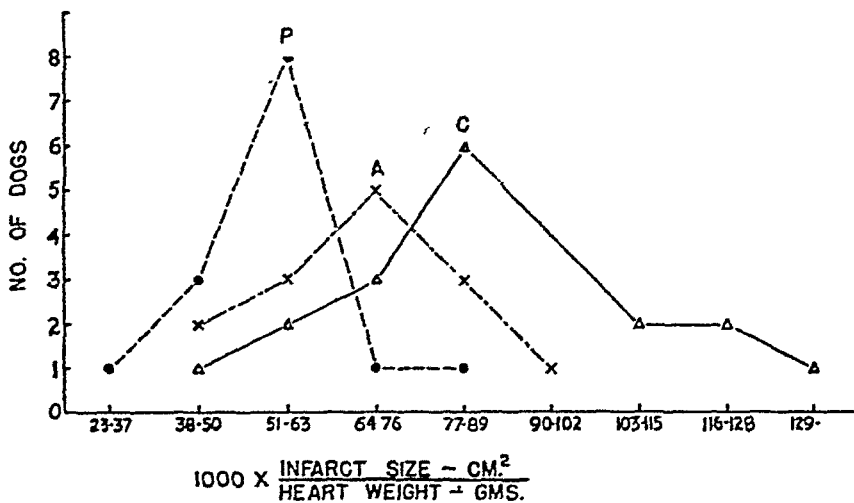


Fig. 2.—The frequency distribution of infarct size per gram of heart weight in the control (Δ - Δ), the aminophylline-treated (\times - \times), and the papaverine-treated (\bullet - \bullet) groups. These are labelled, respectively, C, A, and P. Discussed in text.

2. *Location and Gross and Microscopic Appearance of Infarcts.*—The infarcts were fairly uniform in form and location. The majority were roughly pyramidal in shape with the base of the pyramid located toward the cardiac apex. The infarct involved chiefly the apex and anterior wall of the left ventricle between the anterior papillary muscle and the septum. In larger lesions the anterior papillary muscle and septum were also involved. Occasionally the infarct involved the septum primarily (Fig. 3). In several instances, a narrow portion of the right ventricle adjacent to the septum was also infarcted. The subendocardial layers were involved more extensively than the subepicardial layers. However, there was almost always a thin strip of noninfarcted muscle just beneath the endocardium. In only four hearts were there “through and through” infarcts with pseudoaneurysm formation. The usual location of the infarct is shown in Fig. 4, a photograph obtained in a papaverine-treated animal which survived only ten days and showed at necropsy a soft yellowish-red infarct extending from endo- to epicardium. In general, the involved areas in the animals surviving eight weeks were sharply demarcated (Fig. 3), the ventricular wall was thin, measuring in some parts only 2 to 3 mm., and the muscle was replaced by gray fibrous tissue.

Microscopic analysis of the infarcts in the control, aminophylline and papaverine-treated groups failed to disclose any noticeable difference in the stage of healing in the three groups. A total of ninety-two sections were examined by independent observers without previous knowledge of the identity of the sections; the sections were taken from different regions of the infarcted and normal myocardium. Only four of the forty-six infarcts or 8.7 per cent showed the subacute stage of healing with pigmented macrophages, fibroblasts, and fine collagen formation; these were scattered between the treated and untreated



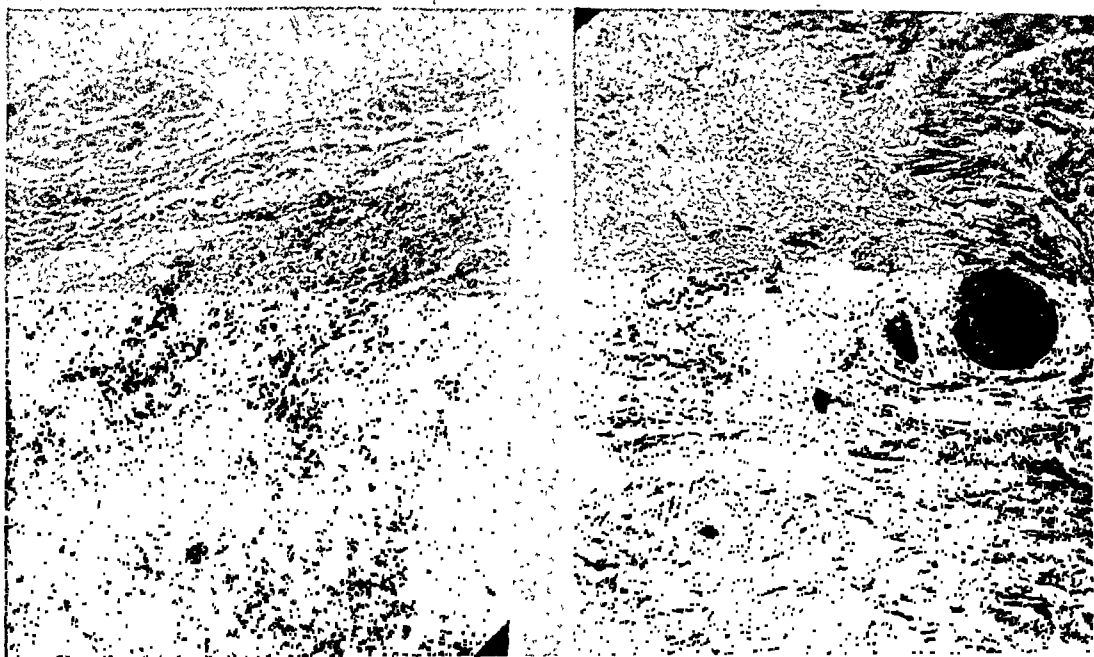
Fig. 3.—View of a dog's heart (12P, Table II) to show the appearance of the infarct eight weeks after ligating the left anterior descending coronary artery. The infarct is in an unusual location, being confined almost exclusively to the septum.



Fig. 4.—Anterior view of dog's heart showing topography of infarcted area resulting from ligation of the left anterior descending coronary artery. Dog survived ten days after ligating left anterior descending coronary artery. The infarcted area is the darker shaded region from the tie to the apex.

groups. All remaining sections showed the advanced stage of healing with compact arrangement of fibroblasts and dense collagen tissue (Fig. 5).

3. *Coronary Anastomoses*.—The anatomy of the coronary arteries of the dog has been adequately described in the literature (Spalteholz,¹¹ Moore,¹² and Pianetto¹³) and in general our observations of sixty-two injected hearts cor-



A.

B.

Fig. 5.—Photomicrographs of myocardial infarcts. *A* shows a field in which a healing (above) and healed (below) infarct is present. Note uninvolved narrow subendocardial muscle, pigment, and dense collagen tissue from above downward. Section taken from Dog 9C, Table II ($\times 75$, hematoxylin-eosin). *B* shows a field in which a healed infarct and injected blood vessels are present. Note injected thickened arteriole in the lower left-hand corner. Section taken from Dog 5P, Table II ($\times 50$, hematoxylin-eosin).



Fig. 6.—Coronary arteries of a normal dog showing predominance of the left coronary artery which is uniformly present in dogs. There are fine anastomoses between the left and right coronary arteries (in the circled area). This is an infrequent finding. Injected with lead-agar mixture.

TABLE III. INCIDENCE AND TYPE OF ANASTOMOSES IN HEARTS WITH INFARCTS EIGHT WEEKS AFTER TIE OF LEFT ANTERIOR DESCENDING CORONARY ARTERY

	CONTROL	AMINOPHYLLINE- TREATED	PAPAVERINE- TREATED	TOTAL
Successful injections	17	13	13	43
Unsuccessful injections	1	1	1	3
Left to left anastomoses*	11	10	11	32
Right to left anastomoses*	0	0	0	0
Convergent anastomoses*	3	2	1	6
No anastomoses	3	1	1	5

*See footnote of Table II. Right to left anastomoses indicates that branches of the left coronary artery are entirely supplied from the right coronary artery.



Fig. 7.—Coronary artery injection of Dog 14P (Table II) from papaverine-treated group, to show L-L anastomoses with retrograde filling distal to site of coronary occlusion made eight weeks prior (shown by arrow). Injected with lead-agar mixture. Infarct = 4.9 cm.²

respond with these descriptions. It should be emphasized that the left coronary artery is uniformly predominant in the dog (Fig. 6), whereas this left dominance occurs in only 20 per cent of human hearts.¹⁶

In Tables II and III are summarized the presence and type of anastomoses encountered in the dogs with coronary ties and myocardial infarcts which survived eight weeks; the terminology followed is that suggested by Schlesinger.⁸ It will be seen that anastomoses developed in the vast majority of cases, but in a few (11.6 per cent) they failed to appear. No instance of right to left anastomoses was encountered, a small number were convergent anastomoses, but in most of the cases the anastomoses were left to left. This is also true in man even in instances in which the right coronary artery is predominant.⁸

There was no correlation between the presence or extent of the anastomoses and the size of the myocardial infarct. Furthermore, no difference was observed between the treated and untreated groups of cases. Nor could any difference be observed in the vascularity demonstrated on injecting lead-agar mixture between the treated and untreated cases. Examples of left to left or convergent anastomoses in three instances of myocardial infarction are shown in Figs. 7, 8, and 9.

While the frequency of anastomoses was not significantly different in the three groups with infarcts, there was clear evidence that in all three groups the presence of the coronary tie for eight weeks had definitely increased the frequency of anastomoses when compared with normal hearts. Thus when the

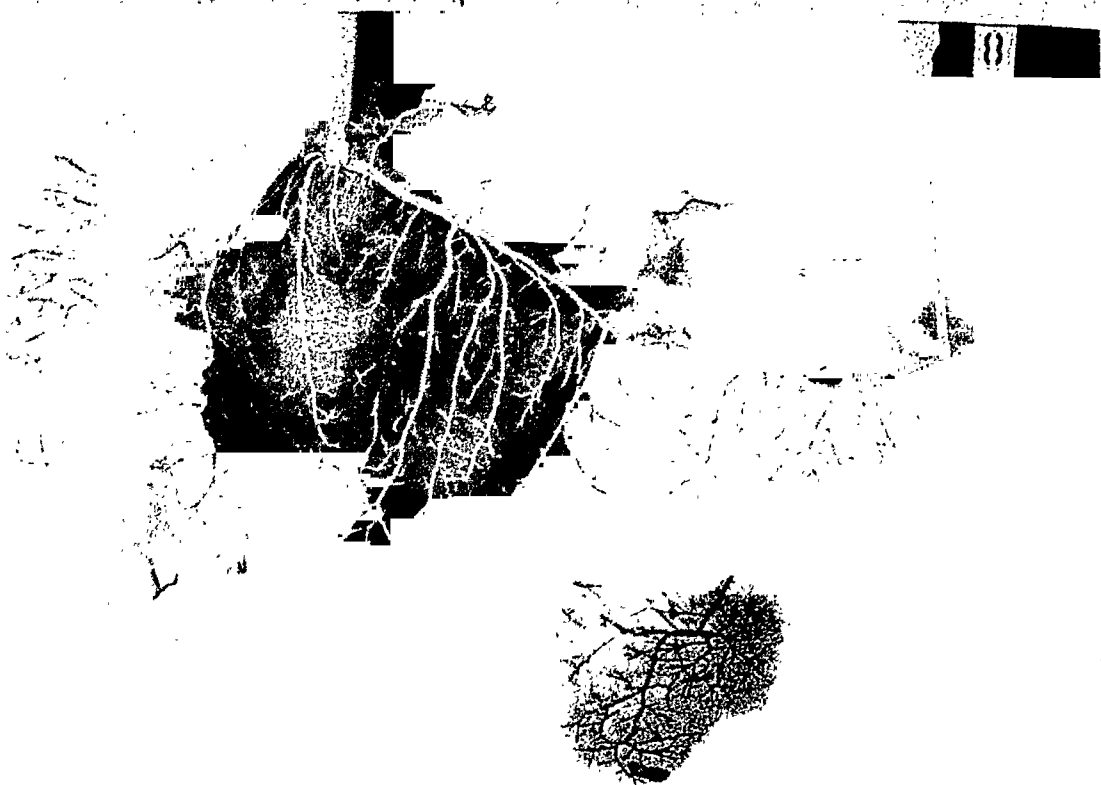


Fig. 8.—Coronary artery injection of Dog 11A (Table II) from aminophylline-treated group to show convergent anastomoses with retrograde filling distal to site of coronary occlusion made eight weeks prior (shown by arrow). Injected with lead-agar mixture. Infarct = 11.1 cm.²

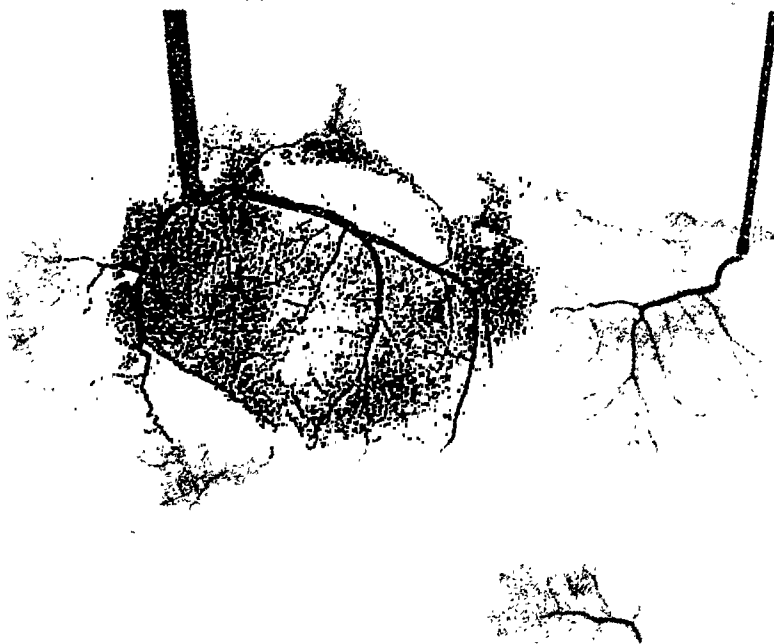


Fig. 9.—Coronary artery injection of Dog 7C (Table II) from control group to show L-L anastomoses with retrograde filling distal to site of coronary occlusion made eight weeks prior (shown by arrow). Injected with lead-agar mixture. Infarct = 11.5 cm.²

entire series of animals surviving eight weeks after coronary tie were compared with a series of animals with ligation post mortem in which the same injection material was used, namely lead-agar mixture, the frequency of anastomoses was strikingly different, viz., 88.4 per cent in the former compared with 13.3 per cent in the latter (Table IV). Two instances of absent anastomoses when injected with lead-agar mixture in these post-mortem ties are shown in Figs. 10 and 11.



Fig. 10.—Coronary artery injection of dog to show absence of any anastomoses distal to site of post-mortem tie of coronary artery (shown by arrow). Injected with lead-agar mixture.



Fig. 11.—Coronary artery injection of dog to show absence of any anastomoses distal to site of post-mortem tie of coronary artery (shown by arrow). Injected with lead-agar mixture.

TABLE IV. COMPARISON OF ANASTOMOSES IN HEARTS WITH INFARCTS EIGHT WEEKS AFTER CORONARY TIE AND NORMAL HEARTS WITH POST-MORTEM CORONARY TIE OF LEFT ANTERIOR DESCENDING CORONARY ARTERY

	HEARTS SURVIVING EIGHT WEEKS AFTER TIE	NORMAL HEARTS WITH POST-MORTEM TIES	
	LEAD-AGAR MIXTURE*	LEAD-AGAR MIXTURE*	LEAD-MERCURY-GELATIN MIXTURE†
Anastomoses	38	2	10
No anastomoses	5	13	4
Totals	43	15	14

*Lead-agar was injected mainly into vessels over 40 micra (see text).

†Lead-mercury-gelatin was injected into vessels between 10 and 40 micra in 70 per cent of cases.



Fig. 12.—Injection of left coronary artery only showing the absence of L-R anastomoses but the presence of L-L anastomoses, with retrograde filling distal to site of post-mortem tie (shown by arrow). Injected with lead-mercury-gelatin mixture.

These findings do not deny that anastomoses will be readily demonstrated in the normal dog's heart if a fine enough injection material is used. The extent of visualization depends on the size of the communicating channels and the size of the particles of the mass used to inject them. When one coronary artery is perfused with saline we have found that the fluid flows out of the other artery. Innumerable anastomotic channels are easily seen on the surface of the heart when India ink is injected into the coronary arteries. However, using the lead-mercury-gelatin mixture, which has smaller particles than the usual radiopaque materials used, and injecting only the left coronary artery under normal pressures (150 to 200 mm. Hg), one does not ordinarily see anastomoses between the left and right coronary arteries (Fig. 12). This is at variance with the observations of Prinzmetal et al.,¹⁰ who were able to inject the entire coronary system in normal human hearts by injecting one branch of the left coronary artery. In the dog, communications between the ventricular branches of the right coronary artery and the right ventricular branches of the left coronary artery can be demonstrated only infrequently. Such an instance is illustrated in Fig. 6. With the lead-mercury-gelatin mixture, however, fine anastomoses

are abundantly demonstrated between the anterior descending, marginal, and circumflex branches of the left coronary artery (Fig. 12).

That the size of the injecting material determines the number of anastomoses demonstrated was shown by comparing a series of fourteen hearts with post-mortem coronary ties injected with lead-mercury-gelatin with a group of fifteen hearts with post-mortem coronary ties injected with lead-agar. As Table IV shows, the percentage of cases with anastomoses in the former is 71.4 per cent compared with 13.3 per cent for the latter. The difference can also be appreciated by comparing Figs. 10 and 11 with Fig. 13.

It was observed over and over again that, when anastomoses are present, the vessel having a tie on it, whether placed there eight weeks before or at post mortem, fills from below indicating the absence of leakage past the ligature.



Fig. 13.—Coronary artery injection showing L-L anastomoses with retrograde filling distal to site of post-mortem tie (shown by arrow). Injected with lead-mercury-gelatin mixture.

It is significant that the lapse of time after ligating a coronary artery makes the demonstration of anastomoses easy even with injection media with larger particles. Our data on animals surviving the coronary tie for less than eight weeks are too incomplete to warrant any statements on the time it takes for collaterals to develop and enlarge. However, we have inadvertently made observations on the effect of pericardial adhesions on these collateral channels. In two instances, a gauze sponge, 4 by 3 cm., was left in the pericardial sac. At necropsy, many adhesions between the scarred myocardium and parietal pericardium could be demonstrated. The hearts with these adhesions failed to reveal any additional vascular channels to the myocardium by way of the adhesions. This is in accord with the findings of the more systematic study of vascularization by pericardial adhesions made by Burchell.¹⁴

DISCUSSION

The fact that myocardial infarcts develop when a single major artery like the left anterior descending artery is occluded shows that the coronary arteries are end arteries even though anastomotic communications can be demonstrated in many instances. While these communications can supply some blood to the region rendered ischemic by coronary occlusion, they are inadequate to make

up entirely for the deficit in blood supply. In this sense, then, the coronary arteries in the dog, and, presumably in man, are end arteries physiologically. Coronary arteriosclerosis tends to alter this condition by stimulating the development of a more adequate collateral anastomotic system so that occlusion of single large coronary artery branches need not lead to myocardial infarction. Myocardial infarcts in the presence of coronary sclerosis usually develop only when more than one of the coronary arteries supplying a region are narrowed or occluded, as earlier work has demonstrated.¹⁵

Our results have shown that coronary vasodilator drugs have an effect on infarct size. Infarcts in papaverine-treated dogs are definitely smaller than those in untreated animals. Aminophylline also has a statistically significant effect, but less striking than that of papaverine. Our experience, therefore, supports the use of such vasodilators in treating recent myocardial infarction. Of course these drugs should be given in adequate amounts and frequently enough so as to have a sustained effect of sufficient intensity. The route of administration chosen should also be one which ensures that the drug gets to the coronary vessels in adequate quantities. Papaverine can be given either orally or parenterally, but in the case of aminophylline the question may be raised whether oral administration is effective. Reduction in the size of the ischemic area is of value in lessening the amount of heart muscle which remains impaired and nonfunctioning and so should lessen the occurrence and extent of heart failure and also the acute coronary insufficiency of the regions of the heart not primarily involved by the occlusion. If generalized, coronary "spasm" accompanies infarction, the vasodilator drugs will also tend to neutralize this effect. Papaverine has other advantages in that it is a mild sedative and is valuable in preventing active ectopic rhythms.^{2, 3}

Although a better blood supply to the heart areas supplied by the occluded coronary artery must be postulated to account for the smaller infarct size in the drug-treated dogs, this could not be demonstrated by injection of the coronary system eight weeks after coronary ligation. Size and extent of the vascular bed to the ischemic area demonstrated by the method employed were of the same order in the papaverine-treated and in the aminophylline-treated dogs as in the untreated ones. There are two possible explanations for this apparent paradox.

First, the size and extent of the vascular bed which was formed to supply the ischemic area at the end of eight weeks gave no clue as to the rate at which this vascularization developed. Examination at the end of eight weeks shows the extent of the maximum blood supply then existing regardless of whether this development took place slowly or rapidly. However, since the enlargement of collaterals appears to depend, among other factors, upon the pressure gradient across the anastomotic communications, those that develop rapidly at first would cause a lowering of the pressure gradient and therefore develop more slowly later in comparison with those that develop sluggishly at first. After a time, therefore, the more slowly developing anastomoses would, as it were, catch up with those which started to develop brusquely. Vasodilator drugs would be expected to facilitate the early rapid development of collaterals by dilating the coronary vessels leading to the communicating vessels. This is due to the fact that such vasodilatation increases the pressure gradient across the anastomosis by lessening the pressure gradient from the aorta to the junctions of these anastomoses with the patent coronary arteries. The earlier development of collaterals in the drug-treated dogs would lessen the ischemia of the peripheral areas of the ischemic region sufficiently to prevent them from becoming necrotic.

The vasodilatation in the drug-treated animals not only facilitates the early growth of anastomotic channels but, in addition, provides a greater blood supply through dilatation of channels already existing. The size of the vascular bed revealed by necropsy injection does not necessarily give the picture existing during life, since it ignores vasomotor tone. Even with the same extent of anastomotic channels, the vasodilator drugs provide a larger bed with a greater blood flow than is present in an untreated animal.

From our results the following conclusions are drawn:

(1) The action of papaverine and, to a lesser extent, aminophylline on infarct size is to provide a greater blood flow to the ischemic area by decreasing the vasomotor tone of the coronary vessels and by facilitating the early development of collateral channels when the ill effects of ischemia can be compensated for most adequately and necrosis avoided.

(2) Collateral circulation is present even before the coronary artery ligation since a large percentage of control animals show injectable channels after post-mortem coronary tie when a medium of small-sized particles like the lead-mercury-gelatin mixture is used for injection. Such channels are found to be increased in size eight weeks after the coronary tie since they are then more readily filled even with larger-sized particles such as found in the lead-agar mixture. The enlargement and development of the coronary collaterals are brought about by the altered pressure gradient following coronary occlusion. Normally there is little pressure drop across these interarterial communications, but following coronary occlusion a marked pressure drop occurs which, operating over a period of time, leads to their enlargement on a purely mechanical basis. This enlargement is, of course, favored by the loss of vasomotor tone consequent to the vasodilator action of local ischemia, and, in the case of the drug-treated animals, it is further facilitated by the vasodilator effect of the drugs.

SUMMARY

1. Papaverine and aminophylline, when given for a period of eight weeks in amounts comparable to therapeutic and nontoxic doses in man, reduce the size of experimental myocardial infarcts in dogs. Papaverine is more effective than aminophylline in this respect.

2. There is an anatomic increase in the size and number of anastomotic channels in infarcted hearts with occlusion of a main coronary artery as compared with normal hearts. This was demonstrated by injection technique.

3. No difference in the stage of healing was seen microscopically between the treated and untreated dogs at the end of eight weeks.

4. The difference in infarct size between the treated and untreated dogs was not associated with any anatomic difference in the post-mortem demonstration of the extent of the anastomoses. It is concluded that the difference in infarct size was, therefore, due to a larger caliber of these anastomotic channels during life in the drug-treated dogs because of coronary vasodilatation and, probably, also to their more rapid early development. In these two ways the marginal area of the ischemic region was rendered sufficiently less ischemic as not to become necrotic.

5. It is concluded that the rationale of early vasodilator therapy in recent myocardial infarction has been demonstrated and that both aminophylline and papaverine, especially the latter, have been shown to be effective.

We are indebted to various members of the department for assistance in the conduct of these experiments, and to Mrs. J. Meyer for her help in the statistical analysis of the data.

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PRIMARY TUMOR OF THE LEFT AURICLE SIMULATING MITRAL STENOSIS

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TUMORS of the heart, though rare, are of considerable interest. Statistics compiled by Mead show that primary tumor of the heart occurred in 0.03 per cent of all autopsies (40,000).¹ The literature on this subject up to 1931 has been thoroughly reviewed by Yater,² and since then by Mead,¹ Gilchrist and Millar,³ and more recently by Lisa, Hirschhorn, and Hart.⁴

The possibility of the existence of such a pathologic state must be considered more frequently in differential diagnosis of heart disease of undetermined etiology. It is only by careful observation, frequent clinical examinations, and accurate followup of cases, with this condition in mind, that more exacting criteria for early diagnosis may be added to the literature. Only two cases have been reported in which the diagnosis was made before death and confirmed by autopsy. In both cases the tumors were malignant.^{5, 6}

Recent reports in the literature⁷ describe the removal of an intrapericardial teratoma as well as a tumorlike mass located in the left ventricle. An advance of this nature in intrathoracic surgery serves to stimulate the reporting of all cases of cardiac neoplasm with the hope that eventually a satisfactory symptom complex for early diagnosis may be achieved.

The purpose of this paper is to present a case of primary tumor of the heart diagnosed as mitral stenosis in a 48-year-old woman. The presenting signs, electrocardiographic and x-ray studies, were confirmatory of this diagnosis. The atypical course during the last few days of life was explained on the basis of unusual complications. It is this atypical course that recently has been re-emphasized as being most helpful in the diagnosis of heart tumor.⁸ Certain pathologic observations made in this case suggest that hemorrhage into the tumor may have originated earlier than might have occurred if the use of digitalis had been omitted.⁹

The following report is of interest in several respects and adds another case of primary tumor of the left auricle to the already accumulated literature.

CASE REPORT

A 48-year-old married woman presented herself to her family physician with complaints of exertional dyspnea, chest pain, cough, weakness, and menopausal symptoms. Physical examination was negative except for a soft mid-diastolic murmur at the mitral area, heard only in the left lateral decubitus and accentuated by moderate exercise. She had been under the care of a competent internist for some time previously. The diagnosis of heart disease was a complete surprise to the patient, as she had been reassured many times concerning her cardiac status. An electrocardiogram taken at this time (Fig. 1) showed regular sinus rhythm at a rate of 100. There was slight right axis deviation. There was a prominent P₂ and P₃. Lead IVF showed a small R₄. There was a tendency to low voltage and some slurring of the QRS complexes.

The x-ray findings (Fig. 2) by Dr. K. L. Mitton were reported as follows:

Examination of the chest showed that the left side of the bony cage was slightly fuller than the right. The aorta was well within the limits of normal in size. There was considerable fullness of the left auricle and in the outflow of the right ventricle. The diaphragms were smooth and the angles were clear. There was an increase in density of the hila which was consistent with pulmonary congestion, and there was generalized stippled increase in the density throughout the chest.

Impression.—Mitral stenosis with slight pulmonary congestion and pulmonary hemosiderosis was present.

The attending physician decided to place the patient on complete rest in bed, and digitalization was attempted. Since this medication was poorly tolerated, a brand of lanatosid-C was substituted. The patient's general condition remained satisfactory during the ensuing week. However, the next afternoon and evening, dyspnea became increasingly severe, even at rest, and the following morning the attending physician received an urgent summons to the home of his patient. She appeared in extremis and was breathless, with cold, damp extremities and marked pallor; the clinical picture suggested peripheral circulatory failure. The blood pressure was 80/60. The pulse was feeble and irregular; the rate was 148. She was admitted to the hospital.

On examination, after hospitalization, the patient was seen in a semiupright position, receiving oxygen by tent and showing extreme restlessness. She was pale, with cold extremities, and apprehensive. She complained bitterly of pain in the lower lumbar spine, referred up to the cervical region and out toward both shoulders. The neck veins were not distended, the heart sounds were mainly regular, with occasional extrasystoles, of good quality and with a rate of 120. A presystolic murmur was detected at the mitral area. The lungs were clear anteriorly, but there was dullness in the right base, and a few râles were heard in this area. The abdomen was tender and moderately distended, and the liver was enlarged 3 finger-breadths below the costal margin. There was no ascites or peripheral edema.

We were faced, therefore, with a seriously ill patient who had an emergency hospital admission. She was presented as a case of mitral stenosis, who had been on bed rest for

one week, more or less completely digitalized, and who, after some minor dyspnea the preceding evening, suddenly went into shock. The natural thought was to review the common complications of mitral stenosis, such as are given by White¹⁰: (1) Pulmonary congestion without heart failure (due to a tight mitral valve); (2) right ventricular failure; (3) auricular fibrillation; (4) embolism either into the arterial circulation or pulmonary in nature, as a paradoxical embolus or from a deep leg vein phlebitis; and (5) paroxysmal tachycardia.

In addition to these considerations the possibility of an abdominal disorder, such as mesenteric thrombosis, or an acute surgical abdomen superimposed on heart failure, was entertained. A ball-valve thrombus in the left auricle was considered as well. However, the abrupt clinical changes from a critical to a greatly improved state tended to rule out mesenteric thrombosis.

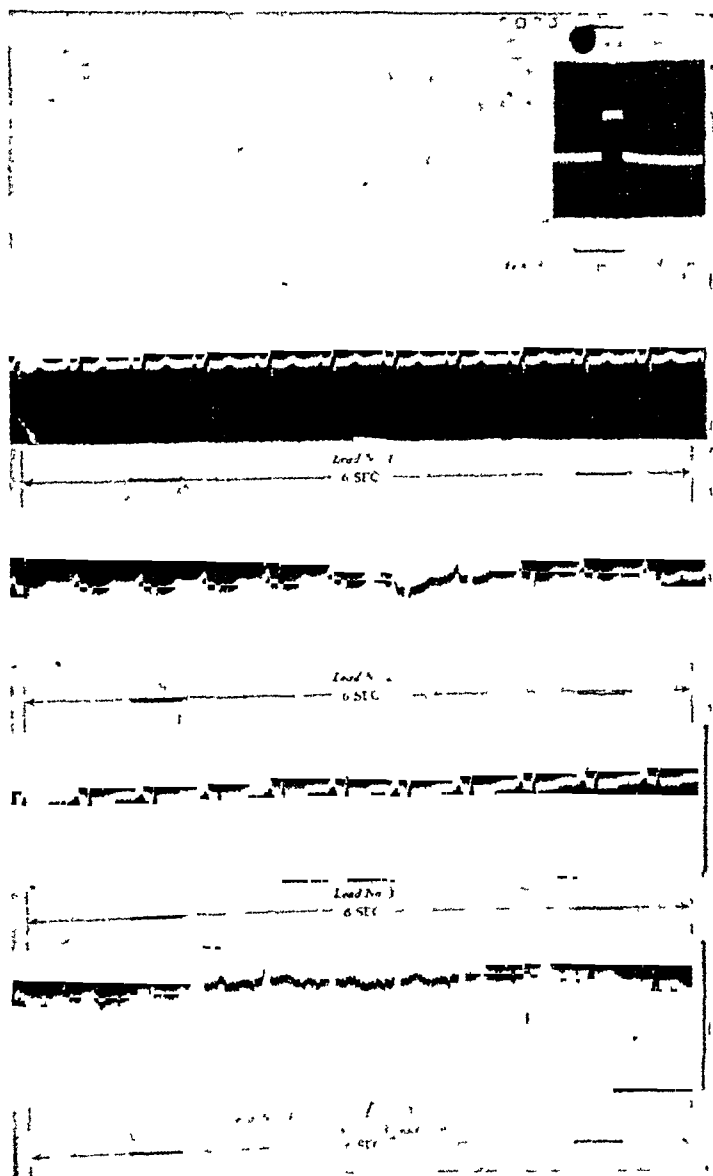


Fig. 1.—Electrocardiogram showing slight right axis deviation and prominent P_2 and P_3 .

Although certain findings of the examination suggested the possibility of pulmonary infarction, others pointed toward right ventricular failure with hepatic engorgement.¹¹ A careful appraisal of the entire picture showed serious contradictions among the signs suggesting either of these conditions. It was difficult to correlate the extremely ill state of the patient with the findings detected on physical examination. On the basis of sudden engorgement of the liver, with absence of distension of the neck veins, the diagnosis of acute right ventricular failure seemed a possibility, especially with dullness and râles in the right base (due to upward enlargement of the liver).¹¹

Since the primary pathologic condition was considered as mitral stenosis, the possibility of associated interauricular septal defect (Lutembacher's disease) with retrograde embolism from the left auricle, its appendage or the mitral valve causing a pulmonary infarction in the base of the right lung or traveling down to block the inferior vena cava and resulting in sudden liver enlargement, was considered.

It was evident that other complications of mitral stenosis, such as embolism somewhere in the arterial circulation, was not a clinical problem and that auricular fibrillation was not present, as the early arrhythmia was transient and due to ventricular extrasystoles. Paroxysmal tachycardia was easily ruled out by the gradual fall in pulse rate.

The patient received active and supportive treatment with oxygen, Coramine, caffeine sodium benzoate, Cedilanid, and small doses of morphine with atropine. During the next twelve hours she seemed improved, her pulse became strong, and the rate began to fall gradually. The following morning she was catheterized and 18 ounces were obtained. The next day she seemed improved and much less apprehensive, the pulse rate was 108, of good quality, and regular. The blood pressure was 107/74. She had rested well during the night and the skin was pink and warm; she had an occasional dry cough, but the lungs were clear. She had been unable to retain fluid, so a clysis of 500 c.c. of saline with 2.5 per cent glucose was given at 10:30 A.M. and 6:30 P.M. She took fluid easily the next day, retaining 1,370 c.c. in twelve hours with an output of only 270 cubic centimeters. Examination showed a distended bladder, and 12 ounces were obtained on catheterization. The back pain had disappeared, breathing was improved, and oxygen was discontinued. The right lung had cleared,

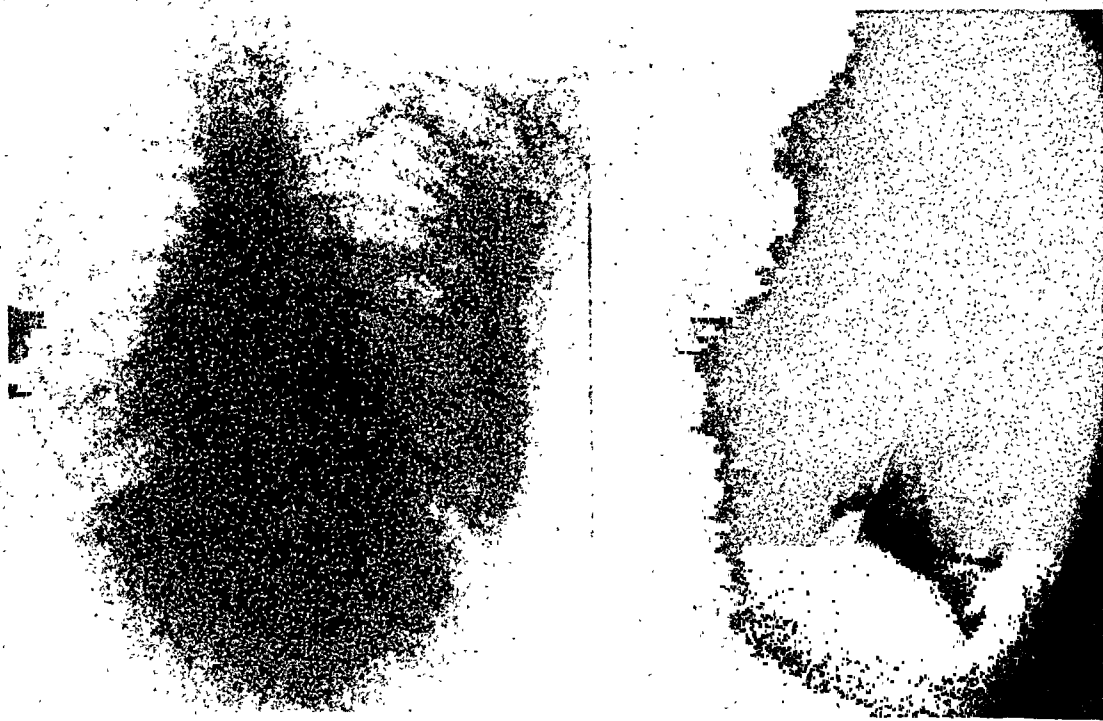


Fig. 2.—Roentgenogram of heart and lungs suggesting mitral stenosis.

the liver was barely palpable, the patient tolerated light nourishment, and during the ensuing twenty-four hours the fluid intake was 1,780 c.c. with 990 c.c. output. Although the general picture suggested gradual but steady improvement, it was apparent she was more comfortable in the upright position. The patient had several sudden attacks in which there was an abrupt transition from reasonable progress to a gravely ill state. When in this condition, the findings were similar to those noted on admission. The following twelve hours the intake was 980 c.c., and the output fell to 0. The admission temperature was 98° F. and rose to 102° F. on the third hospital day. It remained at the level of 100° F. until the death of the patient. The respiratory rate was 30 on admission, fell to 22 on the second day, and remained at this rate until the final episode. Very suddenly the patient had an attack similar to that described on her admission, the pulse became small and feeble, and blood pressure readings were unobtainable. One-fourth grain of morphine seemed to improve her condition rapidly, but a half hour later a similar attack occurred, and the patient died suddenly, six days after being admitted.

Laboratory Findings.—Hemoglobin, 81 per cent; erythrocytes, 4,100,000; leucocytes, 28,000; icteric index, 18; carbon dioxide combining power, 38 vol. per cent; urea nitrogen, 53 mg. per cent. Urine: albumin, 2 plus; sugar, absent; few hyaline casts in the sediment.

Necropsy.—An examination of the body was performed two hours post mortem. The body was that of a fairly well-nourished and well-developed white woman. The face and neck were deeply cyanotic. The pupils were 4 mm. wide, round, and equal. There was no definite jaundice and no edema. When the sternum and the adjacent ribs were removed, the left pleural cavity was found to contain about 500 c.c. of clear straw-colored fluid. No fluid was found in the right cavity. Each pleural cavity was free of adhesions. The heart, when freed from blood clot, weighed 400 grams. It was globular in shape, moderately enlarged, and in diastole. The epicardial surface showed nothing of note. On opening the left auricle a soft but resilient tumor mass was found filling the entire cavity. The tumor consisted of a roughly globular, polypoid growth, 6 by 5 by 6 cm., the external surface of which was slightly lobulated, glistening, grayish green, and devoid of any signs of recent thrombosis.



Fig. 3.



Fig. 4.

Fig. 3.—Photograph showing pedunculated myxoma attached to the interauricular septum of the left auricle.

Fig. 4.—Photomicrograph (X300) of the heart tumor showing delicate blood vessels, fusiform and stellate cells in a mucoid matrix.

It was attached by a broad base to the interauricular septum just above the upper border of the closed foramen ovale (Fig. 3). When first seen the tumor rested snugly in the mitral orifice, but it could be displaced above the valve base. A longitudinal bisection of the tumor showed the base mottled red and brown while the periphery varied from a translucent yellow green to gray and resembled gelatinous material. The ventricles were both moderately dilated, particularly the right one, and the walls of the latter chamber were considerably hypertrophied. The valve measurements were all within normal limits. The cusps and leaflets of all valves showed no evidence of vegetations, and there was no scarring to suggest previous valvular injury. All chambers were free of thrombi. The root of the aorta had a smooth intimal surface. The coronary arteries were thin walled and patent. Both lungs showed an increased firmness, and the cut surface was that of chronic passive congestion. The peritoneal cavity contained no free fluid. The liver weighed 1,350 grams. The capsule was smooth. The cut surface showed the parenchyma pale, golden brownish yellow, and the centers of the lobules were quite prominent. The gall bladder was normal. The remaining organs were examined and showed nothing of pathologic interest except for the effects of circulatory failure.

Anatomic Diagnoses.—The anatomic diagnoses were: tumor of the left auricle obstructing the auriculoventricular orifice; brown induration of lungs; and chronic passive congestion of liver, spleen, and kidneys.

Microscopic (Fig. 4).—Sections of the heart tumor revealed a rather acellular matrix stained with various degrees of intensity, partly eosinophilic and partly basophilic. The cells in the loose network of the intercellular substance were elongated and fusiform in shape. Stellate forms with delicate, anastomosing fibrillary processes were also seen. A small proportion of round and oval cells with distinct cell membranes and compact nuclei were found about capillaries and blood spaces where they occasionally formed radial palisades. Scattered throughout the tumor were multinucleated cells with scant and pale cytoplasm. Wavy elastic fibers were seen in the section stained by the Weigert elastic tissue method. The periphery of the tumor was covered with flattened endothelium-like cells. Extravasation of erythrocytes and numerous hemosiderin-containing phagocytes were found at the base of the tumor. Selected sections through the interauricular wall at the site of attachment of the tumor showed it to originate from subendothelial connective tissue without interruption of the medial elastic fiber network of the endocardium. The vessels in the subendocardial tissue were quite tortuous and had thickened walls. The myocardium revealed no evidence of rheumatic disease.

The lungs showed considerable passive congestion, hemosiderosis, and edema. Signs of passive congestion of longer duration were found in the liver, spleen, and kidneys.



Fig. 5.—Photomicrograph ($\times 300$) showing surface of tumor with endothelial covering and subjacent tissue beneath which is fresh hemorrhage. Note vascularity of the tumor.

DISCUSSION

A tumor found in the heart may be a true neoplasm or a thrombus. Tumors of the heart were observed by the old anatomists and classified as polypi cordis. In 1685, Zollicoferus¹² wrote a dissertation on the subject "De polypo cordis." Richard Link¹³ reviewed the literature from 1824 to 1908 and tabulated ninety-one primary neoplasms of the heart. In 1923, Mandelstamm¹⁴ collected 143 primary tumors of the heart, of which 117 were benign and twenty-six were malignant. Yater, in 1931, brought the total of heart neoplasms to 150 and, in 1941, Lisa, Hirschhorn, and Hart added thirty-three more cases from the literature.

All primary neoplasms of the heart are of mesoblastic origin; fibroma, myxoma, sarcoma, and rhabdomyoma predominating. They occur in any portion of the heart. Myxoma is the most common and the most debated type of cardiac tumor. Thorel¹⁵ believed that myxomas are merely degeneration forms of organized thrombi. In a series of articles on tumors of the heart he analyzed twenty-four cases reported as myxomas and stated that they were all, except one, organized thrombi. Stahr,¹⁶ Karrenstein,¹⁷ and Husten¹⁸ also believed that most endocardial myxomas were thrombi in various stages of organization. Ribbert,¹⁹ on the other hand, is inclined to think that most of the tumors described as myxomas are true neoplasms originating from rests of embryonic mucoid tissue, which persists at times, especially in the rim of the foramen ovale. He emphasized that (1) the masses are usually too large to be organized thrombi, (2) it is difficult to conceive of thrombi forming in otherwise normal hearts not showing the slightest evidence of previous endocarditis or trauma, and (3) myxomas occur exclusively in the auricles whereas thrombi occur just as frequently, if not more so, in the ventricles. Ewing,²⁰ in his book *Neoplastic Diseases*, states that separation of myxomas from organized thrombi may be based on the highly mucinous character of the stroma, and on the presence of orderly radiating blood vessels and elastic fibers. He continues, "it seems unlikely that a simple organizing blood-clot can reproduce the positive features of the true myxoma. Hence the great majority of the reported cases of cardiac myxoma are probably genuine."

Considering our case, the size of the tumor, the site of attachment, the absence of layer formation (as would be expected in a thrombus), the healthy state of the endocardium, and the histologic structure all seem to indicate that the tumor described above represents a true neoplasm. The presence of hemorrhage at the base of the tumor is of recent origin and is easily explained by the delicate structure of the vessels and the mechanical conditions to which the tumor was subjected. Digitalis administration and forced contraction of the myocardium may have been contributory.

Various attempts have been made to classify cardiac neoplasms on a clinical basis, so as thereby to facilitate their diagnosis during life. (Link,¹³ Meroz,²¹ and Yater,² have each proposed classifications.) From a consideration of the case reports, it is apparent that the large intracavitary tumors which are usually of myxomatous and sometimes sarcomatous structure give rise to a group of symptoms which are quite characteristic. Meroz has pointed out that pedunculated tumors arising in the left heart usually present a clinical picture consisting of palpitation, pain in the cardiac region, edema of the lower limbs, and a degree of dyspnea out of proportion to other physical signs. Of the physical signs, two in particular are emphasized. The first sign, which was pointed out by Ludwig,²² concerns the production of mitral presystolic murmur. The obstruction of an auriculoventricular orifice by the tumor retards the blood flow, narrows the stream, and produces the auscultatory phenomena of a valvular stenosis.

Ludwig²² in reporting a case has collected twenty others in which mitral stenosis was diagnosed during life, but at post-mortem examination the obstruction was found to result from the presence of a neoplasm of auricular origin. Several more cases have been reported since.

The second striking feature is the character of the respiratory difficulties described in patients with auricular tumors. It would seem possible that they were produced by the growth mechanically hindering from time to time the

inflow of blood at the entrance of the pulmonary veins, thus producing periods of temporary stagnation in the lung capillaries.

The most characteristic feature is the inability to ascribe a satisfactory etiological cause for the obvious signs of organic heart disease; there is no history of rheumatic fever; digitalis has no effect, and the physical signs may vary in intensity and in character with change of posture, so that in horizontal position only a systolic murmur may be heard, whereas when the patient is erect and the growth tends to sink downwards into the valve orifice a presystolic rumble may be detected. Attacks of intense dyspnea or paroxysms of cyanosis were observed with change of position.

Sudden death is of common occurrence in primary heart tumors, particularly when they arise in the auricle. Death presumably is due to the impaction of the growth in the mitral ring; this ball-valve action effectively obstructs the circulation.

SUMMARY

1. A case of myxoma of the left auricle has been presented in which the diagnosis of mitral stenosis was made ante mortem.

2. Recent advances in intrathoracic surgery have been noted with the implication that the establishment of a symptom complex for early diagnosis of cardiac neoplasm must be obtained.

3. The histology of myxoma and the differentiation of this tumor from organized thrombi are discussed.

4. The pathologic findings suggest that the use of digitalis in this condition may have caused early death of the patient.

5. The hope is expressed that, in cardiac disease suggesting mitral stenosis of unexplained etiology, the diagnostic possibility of a tumor of the left auricle will be considered more frequently.

We wish to thank Dr. Ellis Kellert for the photographs and for other assistance in the preparation of the report.

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ADDENDUM

The complications of mitral stenosis as noted under Reference 10, were listed from the second edition of *Heart Disease* by Dr. Paul D. White. Reference to the third edition shows three other complications that should be added:

1. Pulmonary apoplexy—the result of bleeding from a vessel secondary to the chronic pulmonary hypertension.

2. The frequent occurrence of neurocirculatory asthenia and cardiac neurosis.

3. Hepatic cirrhosis of cardiac origin.

For the sake of completeness and to bring the possible complications of mitral stenosis up to date, these three additional headings are being added.

PAROXYSMAL COMPLETE HEART BLOCK, PRODUCED BY ISCHEMIA OF THE AURICULOVENTRICULAR NODE

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DESPITE our extensive knowledge of conduction in the mammalian heart, the mechanisms that produce intermittent auriculoventricular block in man are not always clear. It is certain that both interruption of the auriculoventricular bundle^{1, 2} and vagal impulses³ can produce conduction disturbances. A hypersensitive carotid sinus,⁴ pharyngeal⁵ or ocular reflex⁶ are clinical examples of the latter. Some difficulties are encountered when these data are applied to paroxysmal complete heart block, a syndrome characterized by periods of auriculoventricular dissociation that alternate with periods during which conduction is normal.

Short episodes of conduction embarrassment have not infrequently been reduplicated by carotid sinus pressure, and their incidence has been reduced by atropine.⁷ However, a hypersensitive reflex mechanism, though present, may not come into play in the spontaneous attacks. Many a patient with a sinus sensitive to pressure never has episodes of heart block. If it does, the effect might have been enhanced by lesions in the bundle.^{8b} Improvement of

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conduction following atropinization may only mean that a constantly present vagal influence upon the bundle facilitated the development of block; whereas the latter was produced by a factor acting directly upon the auriculoventricular system. Attacks of hours duration can hardly have been produced by nervous influences, that is, if we exclude toxic substances, such as digitalis, from our consideration. They must have an intracardiac basis. It is notoriously difficult to correlate the histologic state of the conduction system with its functional ability during life.³³

We have examined the thirty-one cases of paroxysmal complete heart block reported in the literature.⁸ The block could be temporarily abolished by atropine in six instances.^{8c, d, h, p, s} Here the attacks never lasted longer than one to two minutes, usually several seconds. Pressure of the neck produced a short attack of block in one case.^{8c} In six cases the conduction system was examined with considerable care.^{8e, h, i, k, m, n} In one patient with short attacks of block it was entirely undamaged.^{8k} A second case had manifested short attacks of ventricular asystole which were often provoked by swallowing and could be abolished by atropine.^{8h} More than two years before death chronic complete block, not abolishable by atropine, became established. A large calcareous mass had breached the continuity of the conduction system at one place. Vagal impulses "playing upon a highly diseased structure"⁹ offer an adequate explanation for the attacks. The remaining four cases had shown episodes of complete block lasting from several hours to several months. In all four, inflammatory or degenerative lesions were found in or near the conduction system. In one,^{8e} thin-walled blood sinuses had reduced the size of the bundle. In none of these four cases had the continuity of the auriculoventricular connection been breached. In one⁸ⁿ atropine failed to improve conduction; in all four, moreover, the duration of the attacks made a nervous influence highly improbable. Increased filling of the sinuses^{8e} and temporary pressure by, or edema around, the more permanent lesions have been suggested as the cause of the attacks. In two instances^{8i, n} marked narrowing of the small arteries in the vicinity of the conduction system was found. Lewis^{8h} suggested that a "disease of the small vessels" might account for the temporary inability of the bundle to conduct impulses.

We shall present a case of paroxysmal complete heart block in which the attacks were produced by ischemia of the auriculoventricular node, diagnosed by the electrocardiogram.

CASE REPORT

E. S., a 76-year-old newspaper artist, was admitted to the Peter Bent Brigham Hospital on April 17, 1944. At the age of 21 years he had had a fainting attack that lasted a few seconds, following an attempt to take something from a high shelf. In 1942 several toes of the right foot had been amputated because of gangrene. Except for some residual pain in the foot, he continued to be entirely well and active. Four weeks before admission the patient started to have attacks of fainting. They occurred while he was standing at work, sitting at home, or lying in bed. They were not related to any position of the head. Sometimes he noticed giddiness before fainting, but mostly the attacks came without warning. They were not associated with biting of the tongue, passing of urine or feces, or convulsions; they lasted for only a few seconds and were followed by no ill feelings. They occurred once to three times a day, but four days before admission he had ten attacks within twelve hours. In one of these he hurt his chin and jaw.

Physical examination showed an active man. His temperature was 98.6° F. (rectal); respirations, 16 per minute; pulse, 60 per minute and regular; and blood pressure 190/80. He showed no cyanosis, edema, dyspnea, or orthopnea. There was tortuosity of the retinal vessels and tortuosity and hardening of the temporal and radial arteries. No pulsations

could be felt over the posterior tibial arteries, and only very weak pulsations could be felt over the dorsalis pedis arteries. The right cheek showed swelling and bluish discoloration and was tender on touch. There were well-healed surgical scars on the right foot. The apical impulse was just palpable. A Grade 3 systolic murmur was heard over the apical and aortic areas. A_2 was diminished in intensity. The lungs were clear.

The red blood cell count was 4,200,000; hematocrit, 37; Hinton, negative; and blood urea nitrogen, 16 mg. per cent. The glucose tolerance test showed a diabetic curve; the urine contained a trace of sugar. A 7-foot film of the heart showed it to be normal in size, by height-weight ratio, and normal in contour. There was calcification in the aortic arch. The lungs were clear.

Clinical Course.—During the first twelve days the patient had twenty-nine episodes of syncope and three of bradycardia. After that no more attacks occurred. In the long syncopal attacks the initial giddiness was followed by unconsciousness and convulsions; during the short ones there were no objective symptoms. Only rarely did the attacks follow excessive torsion of the neck; usually no event could be related to their onset. They frequently happened while the patient was quietly lying in bed. Pulse and heart sounds disappeared with the onset of giddiness and returned at the end of the attack. Six times digital pressure was applied to the left or right carotid sinus, or to both simultaneously. During the first twelve days this invariably resulted in disappearance of pulse and heart sounds and in giddiness or convulsions, after which the original rate was resumed. The syncope could be produced with equal ease whether the ventricular rate prior to pressure was 75, 40, or 20. Later, pressure on the sinus did not produce more than a moderate degree of sinus slowing, confirmed by electrocardiograms.

The three episodes of extreme bradycardia lasted for thirteen, three, and three hours, respectively. In addition to loud and slow heart sounds, rapid and faint sounds were audible. The blood pressure remained unchanged. Weakness and a sick feeling in the stomach were the only complaints. The third attack was preceded and followed by a period of moderately slow rate (40 per minute), lasting for forty-eight and thirty hours, respectively.

Fainting occurred in the course of normal, slow, and intermediate heart rate. Sometimes a rate of 60 before fainting was found to have changed to one of 20 fifteen minutes thereafter; at other times the opposite was the case. We did not observe the heart rate immediately before and after spontaneous syncope. Changes in rate without intervening fainting also occurred.

On both the second and third days the patient received three 0.6 mg. doses of atropine sulfate by mouth; during the following three days this was increased to five 0.6 mg. doses, after which it was discontinued. The drug had no effect upon the incidence of fainting; nor did it prevent the bradycardia from recurring. On the evening of the fourth day, 1.25 mg. injected intravenously failed to increase the pulse rate, which was 25, but only accelerated the auricles from 60 to 75 per minute. However, it abolished, temporarily, the effects of carotid sinus pressure.

The patient was discharged after three weeks. He resumed his work and was last seen in September, 1944. He had been quite well except for an occasional short spell of giddiness, provoked by looking upward. The heart rate was 70; the rhythm was regular.

Fig. 1.—Standard Lead II during an episode of bigeminy. For interpretation see text. In this and the following three figures each division of the scale represents 0.04 second (abscissa) and 0.1 millivolt (ordinate).

ANALYSIS OF THE ELECTROCARDIOGRAM

We were able to obtain many electrocardiograms and shall give a detailed discussion of their features. When ventricular rates of 60 to 75 were present, normal sinus rhythm was invariably found. Rates of 40 were due to failure of the ventricle to respond to every second auricular impulse. Rates of 20 to 28

were caused by auriculoventricular dissociation, the auricular rate being 60 to 70. Whenever the ventricle responded to auricular impulses the P-R interval was normal (0.17 second). On the tenth hospital day, occasional coupling was found for a period of three hours. There was complete heart block, but when coupling was present the second complex always represented a sequential beat with a constant and normal P-R interval of 0.17 second (Fig. 1). Two tracings were obtained during carotid sinus pressure, applied when the rate was 70. After initial slowing of the auricles with preservation of the normal P-R interval the ventricular manifestations suddenly disappeared and the auricles speeded up somewhat. Release of pressure was followed by return of unchanged sequential beats at 85 per minute.

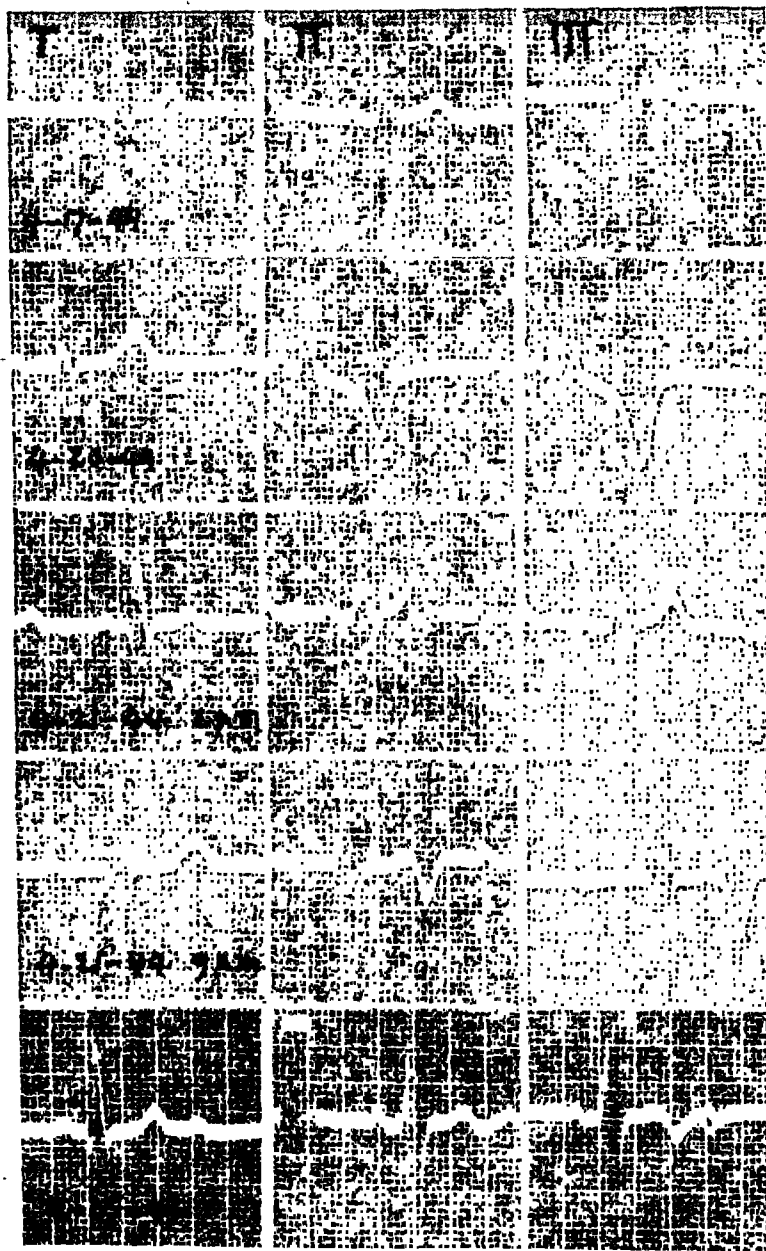


Fig. 2.—Standard leads. First and third rows: normal A-V conduction. Fifth row two-to-one block. Second and fourth rows: A-V dissociation. For interpretation see text.

Two entirely different forms of ventricular complex were found. In the most common one, present on all but one occasion, the initial deflection lasted for 0.14 second (Figs. 2 and 3). It resembles that interpreted by Wilson and his co-workers as right bundle branch block.¹⁰ Unipolar¹² leads were taken from six precordial points¹¹ and from the three extremities. From Fig. 3 it is evident that we are actually dealing with a block in the right bundle branch. During one of the periods of dissociation a different form of complex was

recorded (Fig. 4). Its duration was 0.12 second. The conduction disturbance is probably in the left bundle branch.

Our main interest is centered upon the final deflection. The marked variability of this part of the ventricular complex is evident from Figs. 2 and 3.* With the purpose of expressing the variations in a quantitative way, a method of analysis has been used that was developed by Wilson and his companions.¹³

Whereas the QRS group is the manifestation of invasion of the ventricular musculature by the electrical process (impulse), the T wave is that of its retreat. The former process occupies a shorter time than the latter. If, however, the duration of complete involvement by the impulse ("electrical systole") is the same for each muscle element of the heart, the electrical effect

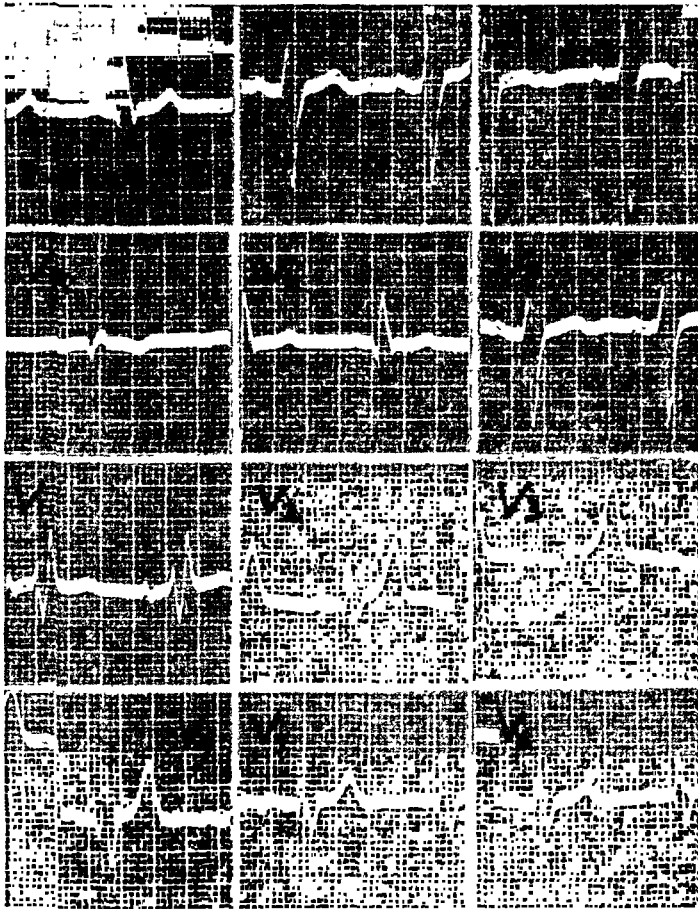


Fig. 3.—Standard leads (first row), unipolar leads from right arm, left arm, and left leg (second row), and unipolar precordial leads from six points during right bundle branch block. The diagnostic features are the double-peaked upward deflection in V_1 and the deep S wave in V_2 to V_6 . The unipolar extremity leads are mixtures of the potential changes occurring on the two ventricular surfaces. Normal A-V conduction.

produced by the heart as a whole during invasion will be the same, though opposite in sign, as that during retreat. In that hypothetical case, the areas of QRS and of T, which are a measure of these effects, will also be the same and of opposite sign, and their algebraic sum will be zero. Deviations from this value are a measure of differences in duration of systole of the muscle elements, as projected on the direction of the particular lead. The vector that represents these deviations can be calculated from the areas of the QRS-T complexes of any two standard leads in much the same way as the instantaneous

*The four electrocardiograms that have not been reproduced resemble those of Fig. 2: The electrocardiogram taken on April 22 resembles that taken on April 21 at 2 P.M.; the one taken on April 24 resembles that taken on April 21 at 2 P.M. but has a higher T_2 and T_3 ; the one taken on April 26 resembles that taken on April 25; and the one taken on April 27 resembles that taken on April 21 at 9 P.M.

electrical axis is obtained. It indicates the direction in which the greatest differences in duration of systole are encountered and points from regions where systole is longest to those where it is shortest. Its size is a measure of the magnitude of these differences. This QRS-T axis has therefore been called "ventricular gradient."^{13a} It is influenced only by local changes of the ventricular musculature.^{13a} The mean axis of QRS and of T, representing, respectively, invasion and retreat during the average moment of these processes, can be calculated in the same way.

All electrocardiograms obtained from our patient were analyzed according to this principle. The practical suggestions of Ashman and Byer^{14a} facilitated the measurements of the surfaces. Three complexes were measured in each of the two standard leads of each tracing, and the average was taken as representative value. Deflections above the isoelectric line were considered positive. Any S-T deviations were considered to be part of the final deflection. Proper corrections were made for errors in standardization. The results are tabulated in Table I.

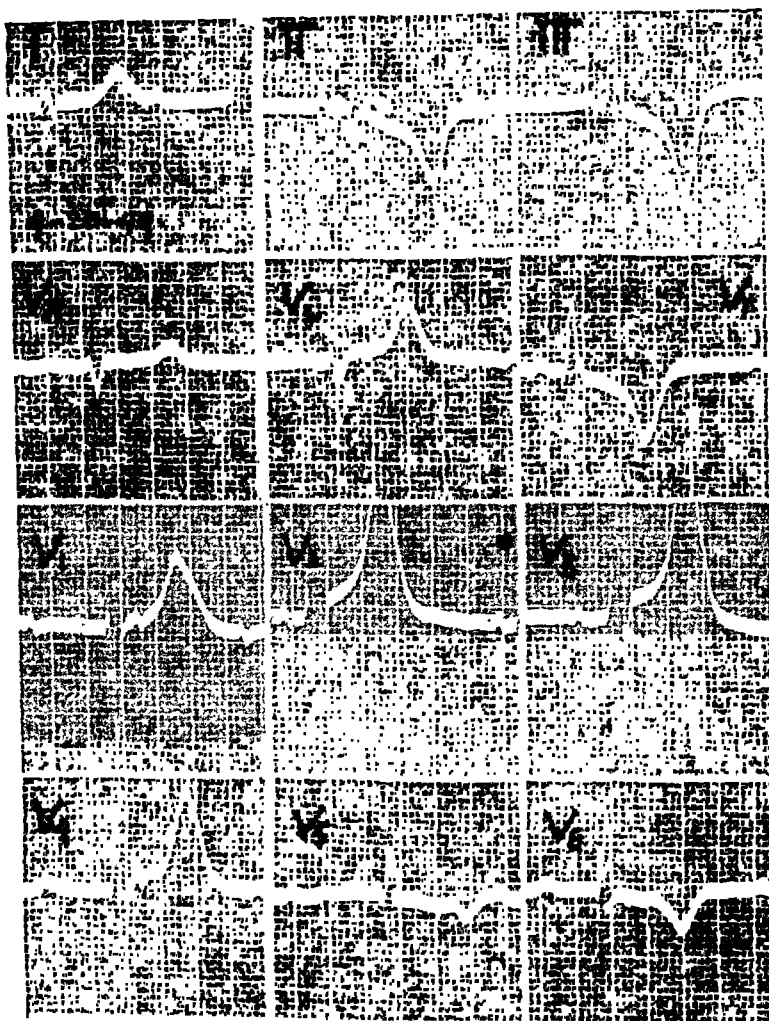


Fig. 4.—Standard leads, unipolar extremity leads, and unipolar precordial leads, probably indicating left bundle branch block. V_1 to V_4 have a normal appearance but are spread out. V_3 shows a bifid R wave. The variations of the right precordium correspond to those of the left arm; those of the left precordium to those of the left leg. A-V dissociation.

INTERPRETATION

Measurements obtained from normal electrocardiograms¹⁴ show that the normal ventricular gradient (A QRS-T) varies from -17 to $+86$ degrees, and from 2 to 94 microvolt-seconds. The mean axis of QRS (A QRS) varies from -30 to $+120$ degrees, and from 1 to 50 microvolt-seconds. It should be clear that, if intraventricular block would constitute the only abnormality in the

TABLE I

NUMBER	DATE	VENTRICULAR RATE PER MIN.	A-V CONDUCTION	INTRAVENTRICULAR CONDUCTION	A QRS		A T		A QRS-T	
					DEGREES	AV-SEC.	DEGREES	AV-SEC.	DEGREES	AV-SEC.
1	4/17/44	55	1:1	R.B.B.B.	-70	80	+39	32	-45	76
2	4/20/44	29	dissociation	R.B.B.B.	+90	52	-75	224	-71	180
3	4/21/44	70	1:1	R.B.B.B.	-75	92	+74	56	-43	56
	2 P.M.									
4	4/21/44	24	dissociation	R.B.B.B.	-71	96	-55	68	-65	160
	9 P.M.									
5	4/22/44	65	1:1	R.B.B.B.	-73	96	+74	56	-43	60
6	4/24/44	75	1:1	R.B.B.B.	-75	108	+82	84	-25	48
7	4/25/44	41	2:1	R.B.B.B.	-71	100	+16	24	-59	108
8	4/26/44	43	2:1	R.B.B.B.	-70	80	+30	36	-46	84
9	4/27/44	25*	dissociation	R.B.B.B.	-72	96	-51	68	-63	164
10	8/15/44	70	1:1	R.B.B.B.	-75	60	+39	28	-46	54
11†	3/23/45	67	1:1	R.B.B.B.	-77	76	+51	11	-70	69
12†	3/29/45	22	dissociation	R.B.B.B. (?)	+17	48	-122	256	-113	220
13†	4/ 3/45	35	dissociation	L.B.B.B.	+74	88	-96	272	-89	186

*Coupling was present.

†See Addendum.

ventricles of our patient, the direction and size of the gradient would be within normal limits, whereas the mean axis of QRS would be abnormal. Our data reveal that direction and size of the gradient as well as of A QRS are abnormal in many of the tracings. The ten tracings can be classified in three groups:

I. Tracings 1, 3, 5, 6, and 10. Gradient varying from -25 to -46 degrees, and from 48 to 76 microvolt-seconds. Normal auriculoventricular conduction.

II. Tracings 2, 4, and 9. Gradient varying from -63 to -72 degrees, and from 160 to 192 microvolt-seconds. Auriculoventricular dissociation.

III. Tracings 7 and 8. Gradient -46 and -59 degrees, and 84 and 108 microvolt-seconds. Two-to-one block.

Though of normal size, the gradient has rotated in counterclockwise fashion in the first five tracings. It has increased to approximately three times its usual size and has further rotated in the same direction in the three instances of complete block. The two tracings of two-to-one block have gradients of an intermediate type (Fig. 5). This rotation indicates either the presence of muscle elements that have developed an excessively long electrical systole and are located caudally to those with unchanged electrical properties;

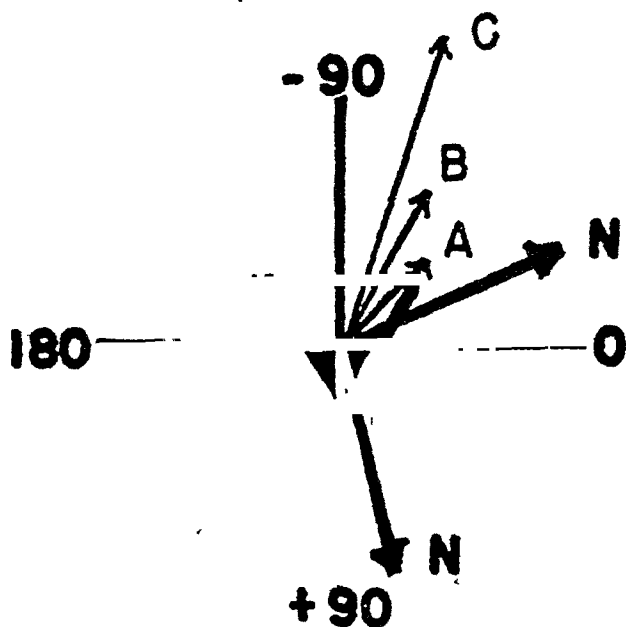


Fig. 5.—Average ventricular gradient during normal auriculoventricular conduction (A), during two-to-one block (B), and during dissociation (C). N-N represents the normal range of direction of the gradient.

or the presence of elements with excessively short systole, located cranially to the unchanged ones. It must have been produced by circulatory changes in the heart muscle as they alone would be able to modify local myocardial function. Now it is known that leads taken directly from the borders of an infarcted area show a prolongation of electrical systole.¹⁶ In human patients, this effect, evident in precordial leads, can persist for months and even years. Moreover it is sometimes the only electrocardiographic evidence of an acute myocardial episode. A similar effect appears immediately after occlusion of a coronary artery, before death or severe damage of muscle tissue has had time to develop; it can be abolished by early restoration of the circulation.¹⁵ This change in duration of systole is most pronounced in the superficial, subepicardial, muscle element.¹⁶ Vascular changes do not produce a shortening of systole.

The observed abnormalities must therefore indicate the presence of a long systole in the subepicardial muscle layer of the posterobasal ventricular wall. It is the only evidence of impairment of blood supply to this area and was

present during the four months that the patient was under observation. It might well have existed for a considerable time prior to admission. It is customary to designate the state of musculature which, deprived of its normal blood supply, produces these electrical changes, by the term "ischemia." A similarly located ischemia can be demonstrated in the chronic stage of posterobasal ("posterior") infarction, where it is accompanied by nonresponding (dead) muscle tissue.

The ventricular gradient on three occasions (tracings 2, 4, and 9) gives evidence of a marked increase in ischemia of the posterobasal wall, that was maintained only for a limited number of hours. The additional rotation is similar to that seen in serial curves after posterior myocardial infarction (Bayley¹⁷ and our own observations). The striking growth is a measure of the increase in magnitude of the forces developed late in systole. In many hearts the degree of vascular impairment, of which it is the evidence, would probably have been sufficient to produce electrical manifestations of more advanced damage: elevation of the S-T segment and decrease in size of the T wave.

It will be noted that the gradient is strikingly the same both during the two periods of right bundle branch block and during the period of left bundle branch block, in spite of considerable differences in the mean axis of QRS. It indicates that factors independent of intraventricular conduction were responsible for the acute changes and were acting with equal intensity during either conduction disturbance. The variability among the five tracings with normal auriculoventricular conduction and particularly the changes in the two tracings with two-to-one block are more than is usually found in myocardial disease. These changes are, in principle, of the same nature as those in the instances of dissociation.

We can conceive the acute ischemia as the result of "coronary failure"¹⁸; that is of a paroxysmal though prolonged disproportion between the blood supply and the demands of the musculature occurring in a region where this supply was already impaired. At no time did the patient complain of angina pectoris. This illustrates the not unusual discrepancy between the degree of vascular impairment and the complaints during life.¹⁸

During the three periods of acute ischemia the patient also showed complete heart block. It is improbable that the two abnormalities occurred independent of each other. No auriculoventricular dissociation without marked deviation of the ventricular gradient was recorded, and vice versa. It is equally improbable that the bradycardia was responsible for the increase in ischemia of the posterobasal wall. If rates of 25 to 30 would be detrimental to myocardial nutrition, the onset of auriculoventricular block should sometimes coincide with the development of angina pectoris or the aggravation of pre-existing heart pain. We have not seen this and have found no reports in the literature. A patient with hypertension whose idioventricular rhythm gradually slowed from 36 to 7.5 per minute complained of progressive weakness, which ended in unconsciousness, but not of pain. The electrocardiogram failed to show changes in the final deflection.^{19*}

The mechanism left to account for the association of the two phenomena is that both were the manifestations of coronary failure. The auriculoventricular connection, especially the node²⁰ is quite sensitive to diminished oxy-

*It should be understood that the relative adequacy of the coronary circulation during bradycardia does not mean that the development of congestive failure could not be facilitated by that of heart block. The cardiac reserve is determined by more factors than only coronary flow, and might well be insufficient in the face of marked increase in diastolic filling as found in complete block. An example of immediate disappearance of congestive failure with restoration of normal auriculoventricular conduction has been found.²¹

gen supply. Decreasing oxygen concentrations in the inspired air cause progressive auriculoventricular block, ending in dissociation in animals and in man.^{21, 22} This occurs in the absence of vagal influences, although vagotomy seems to delay its onset.^{21c}

The simultaneous occurrence of both nodal and posterobasal wall ischemia strongly suggests similarities in blood supply to the two structures. In normal hearts the posterobasal wall of the left ventricle usually receives most of its blood from the right coronary artery. Near the beginning of the terminal (descending) part of the vessel the A. septi fibrosi takes its origin, which sends a fine branch to the auriculoventricular node.²⁴ In only 8 per cent of these hearts the node receives its blood from the left coronary artery.²⁵ Although sclerosis of the coronary vessels can produce pronounced changes in the distribution of blood,¹⁸ clinical proof of the importance of the identical blood vessel to node and posterobasal musculature of abnormal hearts is found in the association of acute myocardial infarction and heart block. Of the sixty cases (fifty-five with complete and five with second degree block) found in the literature, in which the infarct could be localized with certainty, only eight (13 per cent) had involvement of the anterior (anterolateral) ventricular wall²⁶ (Table II).

We conclude that, in our patient, chronic ischemia of the posterobasal ventricular wall was present, as shown by the chronic counterclockwise deviation of the ventricular gradient; that during the episodes of heart block this ischemia increased markedly, as shown by additional rotation and growth of the gradient; and that coincidentally with this an ischemia of the auriculoventricular node developed which resulted in inability of this structure to conduct impulses; both nodal and myocardial ischemia probably being produced by failure of the same artery.

Microscopic changes in the posterobasal wall would not necessarily have been found. From our own observations we noticed that such changes are not infrequently lacking in instances of acute or chronic T-wave inversion, and even in instances of elevation of the S-T segment.

The electrocardiogram reproduced in Fig. 1 shows that the ventricular gradient during the sequential beat was the same as that during the idioventricular beats. Although the reason for the temporary improvement in conduction is not clear (a supernormal phase²⁷ is highly improbable as it would require a P-R interval of 0.9 second), the functional change did not apparently involve a large part of the musculature.

Carotid sinus pressure never resulted in the development of an independent ventricular rhythm but simply suppressed all ventricular activity. This was also observed in the instances where complete heart block had been present previous to the application of pressure. From this we may conclude that the block was localized in the auriculoventricular node and that vagal influences were not responsible for the establishment of auriculoventricular dissociation. The latter is confirmed by our inability to improve conduction with intravenous atropine and by the long duration of the periods of dissociation. On the other hand some of the attacks of giddiness or unconsciousness

TABLE II.

POSTERIOR INFARCTION PROVED BY				ANTERIOR INFARCTION PROVED BY			
ECG	P.M.*	BOTH	TOTAL	ECG	P.M.*	BOTH	TOTAL
34	4	14	52	2	3	3	8

*The post-mortem evidence refers to the finding of massive myocardial involvement.

might well have been due to changes in the degree of block, whereas others undoubtedly were of vagal origin.

It is interesting that carotid sinus pressure failed to produce ventricular asystole as soon as the attacks of heart block stopped. Whereas we are at a loss to explain why the latter failed to return, it is hard to avoid the conclusion that the sensitivity of the reflex mechanism was mainly due to changes in the auriculoventricular node or in the vagal endings around it. A moderate degree of ischemia, not enough to impair conduction, might well have been responsible for it.

DISCUSSION

Except for the cases of myocardial infarction, clinical instances of auriculoventricular block due to deficient oxygen supply to the conduction system are few in number and little convincing. Barach and Woodwell²⁸ described a case of rheumatic heart disease, hypertension, and advanced congestive failure. Delayed auriculoventricular conduction and right bundle branch block were present. Oxygen administration for one-half hour resulted in decrease of cyanosis and "absence of the marked auriculoventricular block" for at least one-half hour. McCulloch²⁹ reported two instances of prolongation of the P-R interval in babies in whom vomiting and diarrhea had resulted in marked dehydration. After improvement the P-R interval returned to normal. Gager¹⁰ found a prolonged P-R interval in a patient with a pericardial effusion. This disappeared after 500 c.c. of sterile fluid had been removed.

The effect of nitrites has been investigated in two instances. Wolferth and McMillan³⁰ were unable to improve conduction with amyl nitrite in a case of paroxysmal heart block. On the contrary the block increased, due to acceleration of the auricles. Lawrence and Forbes³¹ report a case of paroxysmal dissociation. The attacks sometimes lasted for several hours. Inhalation of amyl nitrite invariably abolished the block: normal rhythm with normal P-R interval became established within two minutes and persisted for one-half hour. There was no difference between the final deflection of the sequential beat and that of the idioventricular beat (only the "right pectoral lead" is available for comparison). Gross examination of the heart showed no change in the bundle or any part of the myocardium. There were small atheromatous plaques throughout the coronary arteries, not enough to obstruct the lumen at any point.

The combination of angina pectoris and auriculoventricular block is also rare. Campbell³² mentioned a case in which Stokes-Adams attacks started with severe precordial pain, radiating up the left side to the lower angle of the jaw. Gallavardin³¹ reported three cases in which syncope sometimes was preceded by chest pain. No observations of any kind were made during the attacks. A more convincing report is that of Gallavardin and Rougier.³² A patient with angina pectoris had a prolonged attack of pain. For a month thereafter each attack was followed by syncope and convulsions. The electrocardiograms during these attacks showed auriculoventricular dissociation; between the episodes conduction occurred without delay.

Pathologic evidence of the importance of an adequate blood supply to the node for auriculoventricular conduction is found in two papers by Géraudel.^{33a, c} He carefully examined the hearts of two patients with chronic complete block plus Stokes-Adams attacks and chronic first degree block with attacks of dissociation, respectively. In both cases a normal node and bundle were found, but there was marked narrowing and obstruction of the A. septi fibrosi and of other small arteries.

We have looked for cases of paroxysmal complete heart block associated with growth and counterclockwise rotation of the ventricular gradient, but we found no case comparable to our own. Parkinson, Papp, and Evans³⁴ reported a case of chronic complete block with attacks of ventricular asystole. The electrocardiogram showed right bundle branch block and very deep T_2 and T_3 waves; this is the only instance of its sort. Levine and Matton³⁵ reported ventricular fibrillation which lasted for 3.5 minutes and was followed by a period of ventricular asystole of 1.3 minutes in a patient with chronic auriculoventricular dissociation. She recovered after intracardiac adrenalin. The ventricular gradient before the attack was of normal size and pointed to the left and slightly upward. T_2 and T_3 were inverted. After the attack the gradient had markedly increased in size and had rotated in counterclockwise direction; T_2 and T_3 were more deeply inverted.

The rarity of posterior wall ischemia in chronic and paroxysmal heart block must be ascribed to the size of the lesion which, even when of vascular origin, needs not involve any muscle tissue to cause interruption of the auriculoventricular connection.

SUMMARY AND CONCLUSIONS

A case of paroxysmal auriculoventricular dissociation in a 76-year-old man was described. The three periods of complete block that were observed lasted for thirteen, three, and three hours, respectively. Atropine by mouth and intravenously failed to improve conduction. Pressure on either carotid sinus, applied between attacks, produced ventricular asystole resulting in syncope and convulsions without the development of an idioventricular rhythm. The reflex sensitivity could be abolished by atropine and was undoubtedly responsible for several of the fainting attacks of which the patient complained. These attacks disappeared after the twelfth day of his hospital stay as did also the carotid sinus sensitivity and the episodes of dissociation.

Simultaneously with the dissociation marked changes developed in the final ventricular deflection of the electrocardiogram, which disappeared when conduction again became normal. By determining the ventricular gradient it was found that a severe ischemia of the posterobasal ventricular wall had produced them. A moderate degree of ischemia of the same part of the heart muscle was present during normal conduction for the four months that the patient was under observation.

As it was considered improbable that the bradycardia was the cause of the abnormal state of the musculature it was concluded that both the paroxysmal changes in the final deflection and the simultaneous development of complete heart block were due to coronary failure, resulting in ischemia of the posterobasal ventricular wall and the auriculoventricular node, respectively.

We are grateful to Dr. S. A. Levine, who read the manuscript and made several suggestions.

Addendum.—The patient was readmitted on March 19, 1945, because of increasing pain in his right foot. A film of the foot showed extensive osteomyelitis of the tarsal bones. With rest in bed the pain diminished markedly. On the eleventh hospital day he began to have syncopal attacks and convulsions, during which no pulse could be felt. Between the attacks a pulse rate of 22 to 40 was found, whereas it had been 65 to 80 before this period. Eight convulsive episodes occurred in the course of four hours. Then the pulse rate rose to 70, and the patient was again well. When he was allowed to get up, four days later, the attacks recurred, and continued, often with intervals of only a few minutes, for twenty-four hours. Adrenalin and atropine were ineffective. At the end of this period the patient expired in an episode of asystole.

An electrocardiogram obtained three days after his admission differed from the one taken in September, 1944, in that T_1 , T_2 , and T_3 were very flat. Consequently the ventricular gradient is similar to the mean axis of QRS (Number 11, Table I). A tracing obtained during a period of bradycardia between convulsions (eleventh hospital day) showed complete auriculoventricular block. The ventricular complexes were wide (0.16 second) and, because of the presence of a deep Q_1 , were probably indicative of right bundle branch block. (No precordial leads were taken.) The electrocardiogram taken several hours before death also showed dissociation. The wide (0.14 second) complexes, consisting of a single upward deflection, indicated left bundle branch block.

In spite of great differences in direction and size of A QRS the gradients obtained from the latter two tracings closely resemble each other (Numbers 12 and 13, Table I). As compared with those during previous episodes of dissociation, a rotation to the left and an increase in size have occurred, indicating a more severe (and more extensive) ischemia of the posterobasal wall.

The heart weighed 420 grams. There were some dilatation of the left ventricle and a moderate increase in thickness of the left ventricular wall. No areas of infarction or scarring were seen. Although the coronary arteries were markedly tortuous and calcified, with many atheromatous plaques, no occlusions of the lumina were found. The region of the auriculoventricular conduction system showed no abnormalities. The margins of the aortic cusps were calcified and thickened.

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THE TREATMENT OF AURICULAR FIBRILLATION OCCURRING WITH MYOCARDIAL INFARCTION

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AURICULAR fibrillation occurs as a complication of myocardial infarction in about one in twelve cases¹⁻⁴ (8.3 per cent). No definite criteria have been agreed upon as to its management. It has been regarded by some as usually transient and by others as not apparently altering the prognosis. Any increase of mortality has been ascribed to the associated heart failure or shock, rather than to the arrhythmia. Digitalis and quinidine administration often have been regarded as dangerous and to be considered only as a late, not an early, procedure in treatment.

As a result of varying opinion, one never is quite sure, when auricular fibrillation appears with myocardial infarction, whether to view the arrhythmia expectantly, hoping it will prove to be transitory; whether to ignore it completely, assuming that it will not alter the prognosis anyway; or whether to treat it medically and accept a quantitatively unknown risk from the use of drugs. If one decides to treat it medically, there is uncertainty as to the method of treatment. Should digitalis or quinidine, or both, be used? How soon, how much, and how often? What are the hazards to anticipate as the result of this therapy? These questions arise, and there have been no uniform answers. This is undoubtedly due to the relative infrequency of the arrhythmia which has prevented an adequate analysis of a large series.

In a previous study of eighty-four patients with auricular fibrillation complicating myocardial infarction,⁴ it was found that in the majority the arrhythmia persisted, that the prognosis was worse in the group with persistent auricular fibrillation, and that the prognosis was worse due to the effects of the arrhythmia itself, and not alone to the associated heart damage. It was concluded that an early attempt to eliminate the arrhythmia was indicated unless the risk of the drug used was greater than the risk of the continuance of the arrhythmia. It was found that if congestive failure was associated with the arrhythmia, the use of digitalis alone was apparently harmful, due to production of fatal emboli to the greater circulation. This was tentatively ascribed to several factors, of which persistence of the arrhythmia plus production of an increased constricting expulsive effect upon the ventricle seemed most important.

This is a further clinical statistical study of the data in an attempt to establish tentative positive criteria for treatment. This paper is a study of the results of treatment of these eighty-four patients with auricular fibrillation occurring in 1,247 patients with myocardial infarction admitted to the Los Angeles County General Hospital. We have tried to evaluate the risk of the drug treatment against the natural risk of the condition. Only patients with characteristic electrocardiograms were accepted. Of the eighty-four, seventeen received no medication. The results in these cases served as a control series in indicating the natural course and natural risks in untreated cases. We tried to measure the beneficial effects versus the harmful effects of digitalis and quinidine. The

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primary beneficial objective effects to be obtained in auricular fibrillation from digitalis and quinidine administration were considered as a slower, stronger, ventricular systole and a return of an irregular ectopic rhythm to a regular sinus rhythm. These beneficial effects should be reflected and measurable in an improvement of the mortality rate. The theoretical risks are those of sudden death, embolism, and rupture, and can be determined objectively. The best treatment should be shown, therefore, by a low mortality rate, a high percentage of return to sinus rhythm, and no greater risk of sudden death, embolism, or rupture from the drug than the natural risk from the condition itself.

SUDDEN DEATH AND RUPTURE OF THE HEART

There was no evidence that digitalis increased the mortality by increasing the incidence of sudden death. Quinidine apparently caused three cases of sudden death, but all three were patients with obvious conduction defects, conditions in which the drug should not ordinarily be given (Table I). Rupture of the heart occurred in three of fifty-six patients given digitalis or digitalis and quinidine (5.3 per cent). One patient in seventeen given no medication developed cardiac rupture (5.8 per cent). Rupture of the heart apparently was not a drug hazard in our series.

TABLE I. SUDDEN DEATH OCCURRING IN PATIENTS WITH MYOCARDIAL INFARCTION PLUS AURICULAR FIBRILLATION

TYPE OF MEDICATION	NUMBER OF PATIENTS	NUMBER DYING SUDDENLY	PER CENT
Digitalis alone	44	7	15.9
No digitalis or quinidine	17	3	17.6
Quinidine alone	11	3	27.2
Both digitalis and quinidine	12	0	0
Total	84	13	15.4

MATERIAL

The eighty-four patients, as a group, first were studied as to response to varying medications and to no medication (Table II). The response of the thirty-six patients without congestive failure (Table III) and the forty-eight patients with congestive failure was then determined (Table IV). In order to be sure that congestive heart failure and not peripheral circulatory failure was being treated, only those with objective findings of liver enlargement and ankle edema were included in the congestive failure group.

ADMINISTRATION OF QUINIDINE AND DIGITALIS

The size of the dose of the quinidine and the time interval between doses varied considerably, as the patients were under the care of many different doctors. An average dose was 15 to 20 grains in twenty-four hours. The dose varied from 3 to 6 grains, and the time interval varied from 2 to 6 hours. Thus in very few instances was an optimum effect of quinidine obtained such as would result from a regular administration at 2- to 3-hour intervals. Digitalis was given in no uniform fashion. In the patients with congestive failure, a frequent method of administration was to give the 3 grains of powdered leaf after meals for two to three days. Most of the patients received 20 to 30 grains in three to four days. It is probable that an optimum digitalis effect was obtained in more instances than was an optimum quinidine effect. In most instances no medication was begun until the auricular fibrillation had lasted twenty-four hours or more.

RESULTS

1. *The Group of Eighty-Four as a Whole (Table II).*—Quinidine alone gave the best results, with the lowest mortality and the highest percentage of return to sinus rhythm.

TABLE II. EFFECT OF MEDICATION IN 84 PATIENTS WITH AURICULAR FIBRILLATION AND MYOCARDIAL INFARCTION

(Mortality in Relation to Return to Sinus Rhythm and Incidence of Embolism)

	NUM- BER	AURICULAR FIBRILLA- TION STOPPED	PERCENTAGE RETURNED TO SINUS RHYTHM	NUMBER SYSTEMIC EMBOLI	NUM- BER OF DEATHS	MOR- TALITY (%)	PERCENTAGE OF DEATHS DUE TO EMBOLI
Quinidine alone	11	9	82	0	6	54.5	0
Digitalis plus quinidine	12	9	75	1	8	67	12.5
No medication	17	5	29	2	12	71	17
Digitalis alone	44	6	14	14	41	93	34

2. *The Group of Thirty-Six Without Congestive Failure (Table III).*—Quinidine alone gave the best results, with an equally high percentage of return to sinus rhythm as when quinidine and digitalis were given and the lowest mortality despite three possibly avoidable deaths occurring when quinidine was given to patients with obvious conduction defects. The patients receiving digitalis alone had a smaller percentage of return to sinus rhythm and a higher mortality rate than the patients receiving no medication.

TABLE III. RESULTS OF MEDICATION IN THIRTY-SIX PATIENTS WITH MYOCARDIAL INFARCTION AND AURICULAR FIBRILLATION BUT NO CONGESTIVE FAILURE

	NUM- BER	AURICULAR FIBRILLA- TION STOPPED	PERCENTAGE RETURNED TO SINUS RHYTHM	NUMBER SYSTEMIC EMBOLI	NUM- BER DIED	MOR- TALITY (%)	SUDDEN DEATH (%)
Digitalis and quinidine	5	4	80	1	4	80	0
No medication	9	5	55	2	6	66.6	1 (16)
Digitalis alone	12	3	25	1	9	75	1 (11)
Quinidine alone	10	8	80	0	5	50	3 (60)
Total	36	8	55	4	24	66	

3. *The Group With Congestive Failure (Table IV).*—Of eighty-four patients with congestive failure in addition to the arrhythmia, there were the following findings:

a. If no medication was given, none returned to sinus rhythm, 75 per cent died; none had clinically recognized systemic embolism, but half of the deaths were sudden.

b. If digitalis alone was given only 9 per cent returned to sinus rhythm, 96 per cent died; 41 per cent died of clinically recognized systemic embolism, and 19 per cent of the deaths were sudden.

TABLE IV. RESULTS OF MEDICATION IN FORTY-EIGHT PATIENTS WITH MYOCARDIAL INFARCTION, AURICULAR FIBRILLATION, AND CONGESTIVE FAILURE

	NUM- BER	AURICULAR FIBRILLA- TION STOPPED	PERCENTAGE RETURNED TO SINUS RHYTHM	NUMBER SYSTEMIC EMBOLI	NUM- BER DIED	MOR- TALITY (%)	SUDDEN DEATH (%)
Digitalis and quinidine	7	5	70	0	4	59	0
No medication	8	0	0	0	6	75	3 (50)
Digitalis alone	32	3	9.3	13	31	96.8	6 (19)
Quinidine alone	1	1	100	0	1	100	0
Total	48	9	18.7	13	42	80.7	

c. If digitalis plus quinidine was given, 70 per cent returned to sinus rhythm, 59 per cent died; none had systemic embolism, and none died suddenly. The single patient treated with quinidine alone can be excluded.

SUMMARY OF FINDINGS

1. Digitalis administration did not induce sudden death or cardiac rupture in a significantly higher percentage than no medication.

2. Digitalis was apparently harmful when given alone in both the group with congestive failure and the group without congestive failure.

3. Digitalis alone was harmful apparently because it prevented a spontaneous return to sinus rhythm in the group without congestive failure, and because it induced fatal systemic emboli in the group with congestive failure.

4. Quinidine alone was harmful only when given in the presence of obvious conduction defects.

5. Sudden death could not be correlated with the use of either drug save in the three cases with obvious conduction defects.

6. Although sudden death occurred if no medication was given, or if digitalis alone or quinidine alone was given, it occurred in none of the twelve patients given both digitalis and quinidine.

7. In the group with no congestive failure, quinidine alone gave better results than no medication or digitalis alone.

8. In the group with congestive failure (excluding the single case given quinidine alone) the worst results were from digitalis alone. Thirty-one of the thirty-two patients died (96.8 per cent).

Thirteen of these were due to emboli to the greater circulation. The best results were from combined digitalis and quinidine. In this group there was the lowest mortality, the greatest percentage of return to sinus rhythm, and no sudden deaths from embolism.

DIGITALIS AND QUINIDINE

Theoretically digitalis and quinidine should act as buffers against each other's action tending to induce an ectopic ventricular rhythm. Digitalis is capable of inducing paroxysmal ventricular tachycardia, an arrhythmia which quinidine can prevent; conversely, digitalis is believed to prevent ventricular tachycardia arising from the use of quinidine in the treatment of auricular fibrillation. This reciprocal effect may or may not have been responsible for the absence of sudden death in any of the twelve patients who received both digitalis and quinidine.

DISCUSSION

It is fallacious to generalize from a statistical analysis of a numerically small group. The group studied is numerically small. It represents a group culled from many years of admissions to a large general hospital, however, and establishes some deductions referable to this group which may or may not prove to be generally true. Certain deductions seem fairly obvious. Quinidine alone should not have been given to the patients with obvious conduction defects. This contraindication is generally recognized. Digitalis alone apparently should not have been given to the patients with congestive failure. The incidence of fatal emboli associated with the use of digitalis alone in the patients with congestive failure was too high to be explained upon the basis of chance alone. Early elimination of the auricular fibrillation would have been advisable in view of the correlation of the increased incidence of fatal systemic emboli with

the prolongation of the arrhythmia. The longer the auricular fibrillation was allowed to persist, the greater became the hazard of embolism. The risk of embolism apparently was not in reverting the auricular fibrillation to sinus rhythm but in allowing the auricular fibrillation to persist. The duration of the auricular fibrillation seemed to be related directly to the tendency to fatal emboli. Of eight patients with known pre-existent auricular fibrillation, seven died, of whom five died from emboli to the greater circulation. Of thirty-six patients who had auricular fibrillation at the onset of the attack and who died within seven days with persistent auricular fibrillation, only seven died of fatal emboli. But of thirteen patients in whom the auricular fibrillation persisted over seven days, nine died of fatal systemic emboli. The practical problem of treatment in this whole group of 84 was the treatment of those 49 patients in whom auricular fibrillation was found in the first electrocardiogram, and presumably developed the arrhythmia coincident with the attack. Only two of these forty-nine reverted to sinus rhythm, and forty-two of forty-nine died (85.7 per cent). There was no particular problem in the treatment of those patients who developed auricular fibrillation definitely after the attack. In these patients, the arrhythmia was usually transient and the mortality only slightly increased. Usually no congestive failure was present, and quinidine alone gave the best results (Table III). Of thirty-five patients who developed auricular fibrillation definitely after the attack, only eight persisted in the arrhythmia. In six of the thirty-five patients no medication was given, and in four of those six the arrhythmia disappeared in twenty-four hours. In the absence of congestive failure, it would seem permissible to wait twenty-four hours to see if the arrhythmia is transient. The group of patients in whom the auricular fibrillation was found in the first electrocardiogram, however, usually had had severe previous cardiovascular disease, and a large percentage had congestive failure. Theoretically, treatment directed at elimination of the arrhythmia as well as improvement of the ventricular systole should give the best results. This should be accomplished by giving both quinidine, to revert the ectopic rhythm to sinus rhythm, and digitalis, unless the dangers of the drugs are greater than the danger of the continuing arrhythmia. The risks of quinidine and digitalis given together in this series were less than the risks of no medication. Where they were given together for congestive failure, sinus rhythm returned in a high percentage, and the mortality was low (59 per cent). The group is small but corroborates the theoretical prediction. Therefore, we believe that both digitalis and quinidine should have been given immediately when auricular fibrillation was found in the first electrocardiogram if congestive failure was present. Our data show that if digitalis alone was given, the mortality was 97 per cent. If there was no medication, the mortality was 75 per cent; but if both digitalis and quinidine were given, it was 59 per cent. The use of quinidine in congestive failure ordinarily is considered contraindicated. In the congestive failure associated with auricular fibrillation in myocardial infarction, however, it would seem especially to be indicated for the following reasons: Factually, (1) digitalis alone proved to be dangerous; it increased, rather than decreased mortality; and (2) digitalis plus quinidine proved to be superior; and theoretically, (3) a quick return to sinus rhythm should: (a) prevent further auricular thrombus formation and forestall embolism, and (b) reduce the ventricular rate after the usual initial acceleration.

What other measures may be justifiable in such a desperate situation with 97 per cent mortality, that is, auricular fibrillation and congestive failure occurring in the early days of the infarction (?). Auricular anoxemia and vagal

activity seem to be the factors involved in the production of the arrhythmia in the experimental animal.⁵ In addition to oxygen to relieve anoxemia, the use of atropine as an adjuvant to quinidine may well be considered. Lewis⁶ says the end result of both atropine and quinidine are the same in their action toward auricular fibrillation, only that atropine has a far less powerful effect. They both depress vagal activity, tend to prolong the refractory period, and depress the auricular rate.

LeRoy and Snider,⁷ Falk,⁸ Gilbert,⁹ and Rathe³ already have strongly advocated atropine in myocardial infarction to counteract reflex vasospasm acting through the vagus.

Korns¹⁰ believes it deserves an extended clinical trial because of this action alone. For the auricular fibrillation occurring synchronously with the onset of myocardial infarction where the mortality is nearly 100 per cent, a dual beneficial action would be welcomed. Atropine would seem to deserve a trial here, too.

THE PROGRAM OF MEDICATION

As a result of these data, our general scheme of management of auricular fibrillation occurring with myocardial infarction in the future will be that of an immediate attempt to stop the arrhythmia by the administration of optimum doses of quinidine unless (A) the electrocardiogram shows conduction defects or (B) the arrhythmia occurs several days after the onset of myocardial infarction, and no congestive failure is present. In the latter instance we should wait twenty-four hours to see if there is a spontaneous return to sinus rhythm. If congestive failure is present both quinidine and digitalis will be given at once. Quinidine will be given every two hours in 6-grain doses if there is no hypersensitivity to the initial 3-grain dose. The administration of digitalis alone in such cases will be especially avoided, as we feel it is contraindicated. If auricular fibrillation occurs coincidentally with the attack of myocardial infarction, in addition, we shall give atropine sulfate in an initial dose of $\frac{1}{50}$ grain (1.3 mg.) intravenously and follow by $\frac{1}{150}$ grain (0.5 mg.) by mouth three times daily. These measures seem rational. Only clinical statistical data can prove their value.

SUMMARY AND CONCLUSIONS

1. Auricular fibrillation occurring with myocardial infarction in eighty-four patients represented a definite hazard if allowed to continue.
2. Digitalis alone was apparently harmful whether used in patients with or without congestive failure.
3. Digitalis and quinidine together gave the best result when used in patients with congestive failure plus auricular fibrillation. This was based upon the criteria of mortality rate, return to sinus rhythm, and incidence of occurrence of embolism, rupture, or sudden death.
4. Quinidine alone was adequate if no congestive failure was present.
5. If these data apply generally, digitalis alone should not be given for auricular fibrillation occurring with myocardial infarction. Quinidine plus digitalis should be preferable.
6. A tentative program for medication is suggested.

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THE VALUE OF LEAD IVF IN CARDIAC INFARCTION

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IN THE past, the three standard limb leads frequently have proved inadequate when electrocardiographic confirmation of a clinical diagnosis of cardiac infarction was desired. This led Wolferth and Wood¹ to add the anteroposterior chest lead to the electrocardiogram in an attempt to increase its diagnostic value in this condition.

Normal values for the potential variations in chest leads were later established by Hoffman and DeLong,² Katz and Kissin,³ Goldbloom,⁴ Master,⁵ Rosenblum and Sampson,⁶ Shipley and Hallaran,⁷ and Sorsky and Wood.⁸ To standardize the information obtained from various sources, a Joint Committee of the American Heart Association and the Cardiac Society of Great Britain and Ireland was appointed. The recommendation of this Committee⁹ that, if a single precordial lead be done, Lead IVF (apex-left leg) be the derivation of preference, has been followed at the Toronto General Hospital since Jan. 1, 1938.

Many investigators have emphasized the fact that multiple chest leads are essential to complete electrocardiographic examination of the heart. No single precordial derivation will give the maximum information in all forms of heart disease. However, as a matter of routine in practice, it is seldom feasible to record more than four or, at the most, five leads in a single electrocardiogram. Most routine electrocardiograms of recent years consist of the standard limb leads and Lead IVF. It should be kept in mind that this chest lead was recommended chiefly for its value in anterior cardiac infarction and that other precordial derivations may contribute to the diagnosis of other cardiac conditions much more fully than Lead IVF.

The characteristic changes in chest leads in serial records of cases of recent infarction of the anterior wall of the myocardium have been described in detail.^{1-3, 10-20} Since changes in the QRS complex in Lead IVF are important in the differential diagnosis of infarction from other forms of heart disease, a review of QRS complexes in CF leads in normal hearts may bring abnormal findings into sharper focus* (Fig. 1).

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* In CF, the precordial electrode is placed in the fifth left intercostal space in the mid-clavicular line irrespective of the size or position of the heart, whereas in IVF the electrode is placed on the outer border of the cardiac apex.

QRS Complex in Normal CF Leads.—As the chest electrode travels from CF_1 to CF_4 , i.e., from the right border of the sternum in the fourth intercostal space to the left midclavicular line in the fifth intercostal space and thence, at this same horizontal level, to the anterior axillary line (CF_5) and midaxillary line (CF_6), the QRS complex goes through the changes outlined in Fig. 1. The small initial upward deflection (R) present in CF_1 , rises progressively so that,

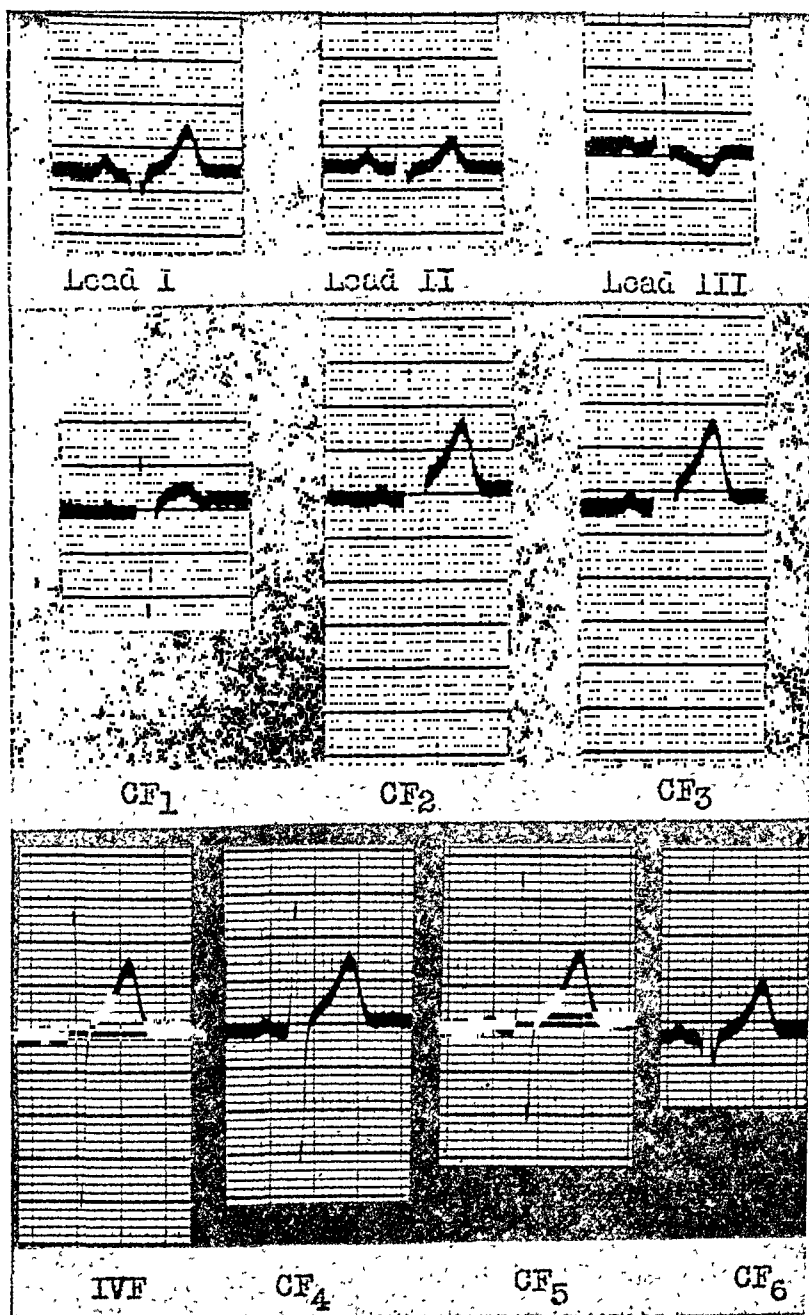


Fig. 1.—The standard limb leads and CF derivations from a young man with no evidence of heart disease.

in CF_4 , R and S waves are usually about equal in magnitude. Farther to the left, the R wave remains high while there is a progressive diminution in the depth of the S wave until the latter may disappear entirely. Usually just before the S wave disappears an initial negative deflection (Q) develops; this deflection is seldom greater than 1 to 2 mm. in depth.

In the presence of recent infarction of the anterior wall of the myocardium, the initial QRS deflection in Lead IVF usually becomes negative (development

of a Q_4) associated with a marked reduction or complete disappearance of the R wave. The S wave remains a deeply negative deflection so that QRS_4 usually becomes wholly negative (Figs. 2 to 7). Less frequently R_4 remains the initial QRS deflection. When this occurs, R_4 is usually small, under 2 mm. in height, but may be somewhat higher or even of normal height (Figs. 4, *b*, *c*, *d*, and *e*). Early in the course of the infarction the RS-T segment is markedly elevated, giving place, in a few days, to a negative T wave of symmetrical limbs, which may become very deeply negative (Fig. 5, *f*).

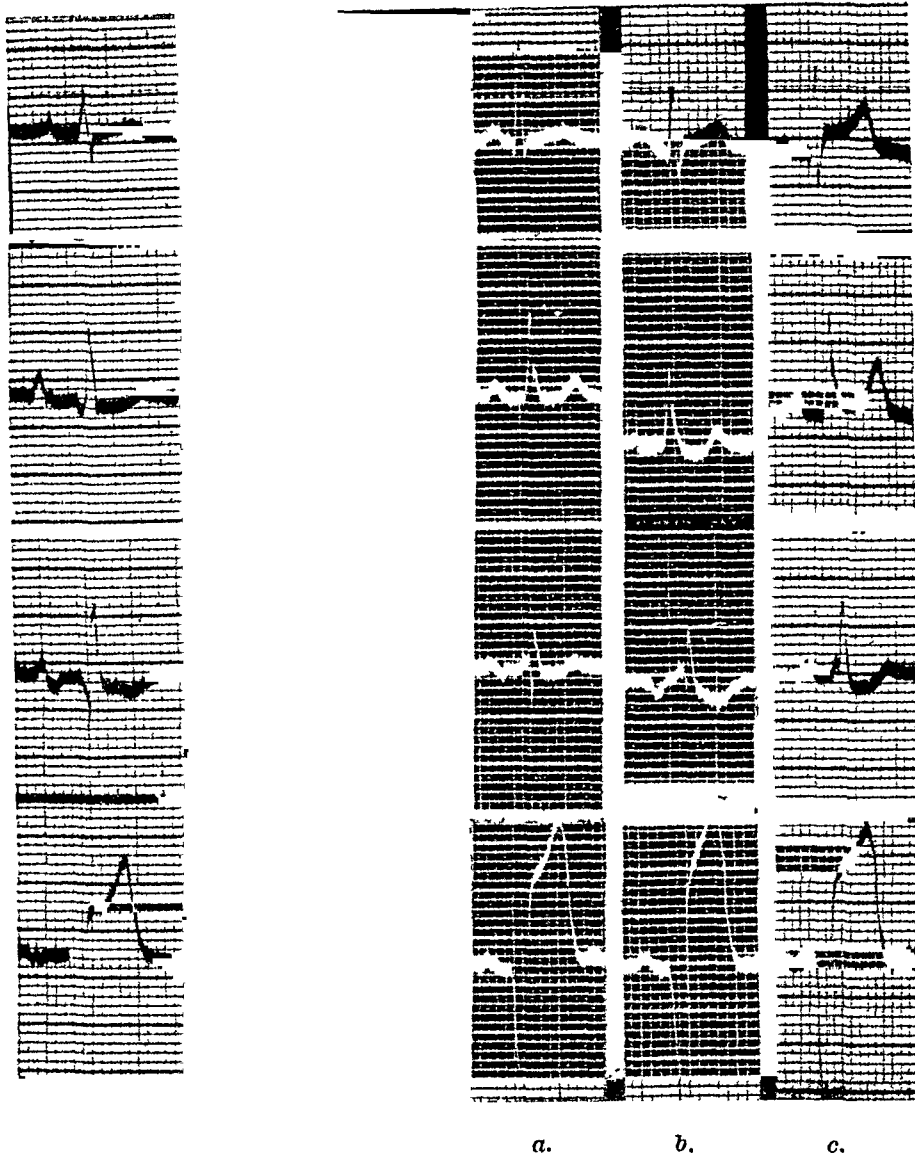


Fig. 2.

Fig. 3.

Fig. 2.—W.B., Feb. 16, 1940. Angina pectoris for one year. Prolonged pain Feb. 7, 1940. A good example of the value of Lead IVF in the diagnosis of recent anterior infarction (confirmed at autopsy Feb. 19, 1940) in the only record obtained. While there is slight depression of the RT segment in Lead III, there is no finding in Lead I that would contribute to the diagnosis.

Fig. 3.—G.H., June 27, 28, and 29, 1940. Angina pectoris for one year. Prolonged pain June 24, 1940. The diagnosis of recent anterior infarction in the initial record depends entirely on the Lead IVF findings of marked elevation of the RT segment associated with absence of the R wave. The diagnosis is obvious in the limb leads in the second and third records. (Diagnosis confirmed at autopsy June 30, 1940.)

Usually, in anterior infarction, in the presence of an entirely negative QRS complex in IVF, a notching of the descending limb can be seen (Fig. 4, *a*). According to Mortensen,¹⁴ this represents the remnant of the R wave which has been reduced to this degree. This notch may be of value in helping to differentiate anterior infarction and left ventricular hypertrophy which, rarely, may be responsible for the absence of the R wave in CF_4 . When this does occur, no semblance of R_4 remains.

Since the development of a Q wave in Lead IVF is important to the diagnosis of anterior infarction, it occasionally becomes necessary to distinguish between a normal and an abnormal Q wave. A normal Q wave (less than 2 mm.) is usually associated with a high R wave and a small or absent S wave (Fig. 1). In the CF₄ position this may obtain normally with a small, centrally placed heart. On the other hand, the Q wave of anterior infarction usually is accompanied by marked reduction in the height of R₄ while the S wave remains deeply negative.

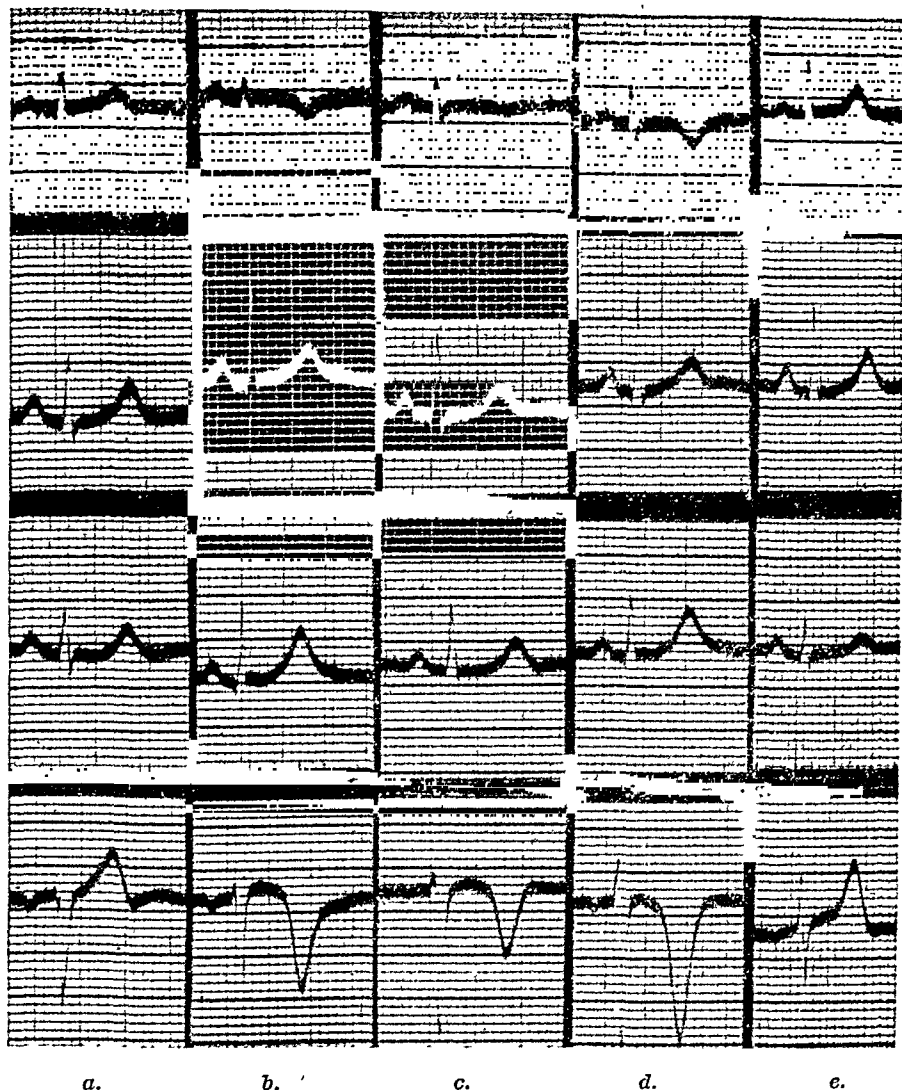


Fig. 4.—P.G., Jan. 12, 13, 17, and 31, 1939, and Feb. 21, 1940. Angina pectoris for two years. Prolonged attack Jan. 12, 1939. The sole diagnostic feature of the initial record is the absence of the R wave in Lead IVF, although there is suggestive depression of the RT segment in Lead III. The diagnosis is obvious in both limb leads and in Lead IVF in the next three records made during the three weeks following the attack of prolonged pain. Complete reversion to a normal record has taken place one year later. (See follow-up group.) At post-mortem examination (Aug. 23, 1940) fibrosis in the apex of the left ventricle was found.

MATERIAL

All cases of cardiac infarction admitted to the public wards of the Toronto General Hospital in a four-year period, 1938 to 1941, have been reviewed. Electrocardiographic records were made at frequent intervals on the majority of cases of recent infarction. In addition to the study of cases of cardiac infarction, all records showing abnormalities in the ventricular complex were reviewed. This latter study was confined to the first thirty months of the four-year admission period, and only the records of those cases coming to autopsy

were selected for analysis and comparison with the series of proved cases of anterior infarction.

All records were taken on an English Cambridge electrocardiograph. Each of the four leads was standardized so that a difference in potential of 1 mv. was recorded by a deflection of 1 cm. in the finished electrocardiogram. The chest electrode consisted of a metal disk, 3 cm. in diameter, which was firmly held to the selected spot by a rubber band encircling the chest.

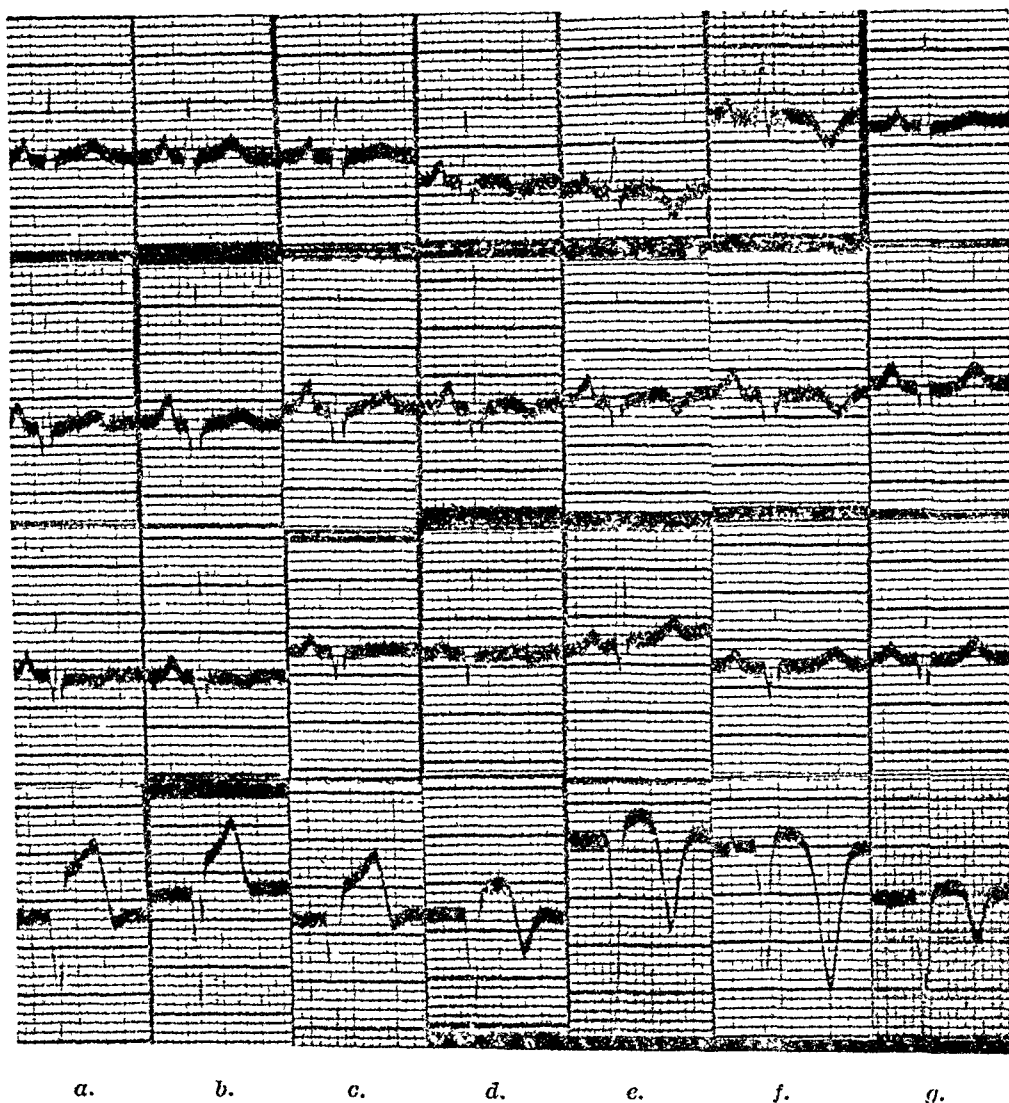


Fig. 5.—W.D., March 20, 23, 25, and 28 and April 1 and 8, 1939, and May 21, 1940. Attacks of precordial pain, March 17 and 18, 1939, followed by fever, leucocytosis, and pericardial friction rub. Lead IVF alone shows indisputable evidence of recent anterior infarction in the first three records taken during the first week after the attacks. During the second and third weeks, the limb leads also show typical diagnostic changes. However, the sole residual evidence of the infarct fourteen months later is to be found in the absence of the R wave and the negative T wave of symmetrical limbs in Lead IVF.

Most of the records were taken by the technician who was instructed to attempt to locate the apex beat by palpation when doing Lead IVF and to place the chest electrode on the outer border of the impulse. If no apical impulse could be palpated, the electrode was to be placed in the fifth left intercostal space in the midclavicular line. Thus, in this study, Lead IVF is a combination of true Lead IVF and Lead CF.

Cases of cardiac infarction were arbitrarily divided into "recent" and "old" groups for the purpose of analysis of the electrocardiograms. A case was considered recent if a record was obtained within one month following the acute attack; otherwise, it was included in the old group.

The group of recent infarctions was subdivided into four classes: (1) anterior, (2) posterior, (3) multiple or extensive, and (4) atypical. The cases of old infarction were subdivided into anterior and posterior groups for

further study. Included in the group of old anterior infarcts are many cases in the recent group recalled for further electrocardiographic study.

Recent Anterior Infarcts.—As shown in Table I, 152 cases of recent anterior infarction were analyzed and grouped into four subdivisions:

TABLE I. RELATIVE DIAGNOSTIC VALUE OF LEAD I AND LEAD IV IN 152 CASES OF "RECENT" ANTERIOR INFARCTION

DIAGNOSIS CONFIRMED BY	NUMBER OF CASES	INITIAL POSITIVE DEFLECTION, QRS ₁		
		ABSENT	SMALL	NORMAL
a. Lead IV only (29 cases):				
Examined post mortem	9	7	2	0
Clinical diagnosis only	20	20	0	0
b. Lead IV superior to Lead I (35 cases):				
Examined post mortem	8	5	2	1
Clinical diagnosis only	27	25	2	0
c. Leads I and IV equal (76 cases):				
Examined post mortem	15	12	2	1
Clinical diagnosis only	61	57	3	1
d. Lead I only (12 cases):				
Examined post mortem	2	0	0	2
Clinical diagnosis only	10	0	0	10
Total number of cases	152	126	11	15
Total number of cases examined post mortem	34	24	6	4

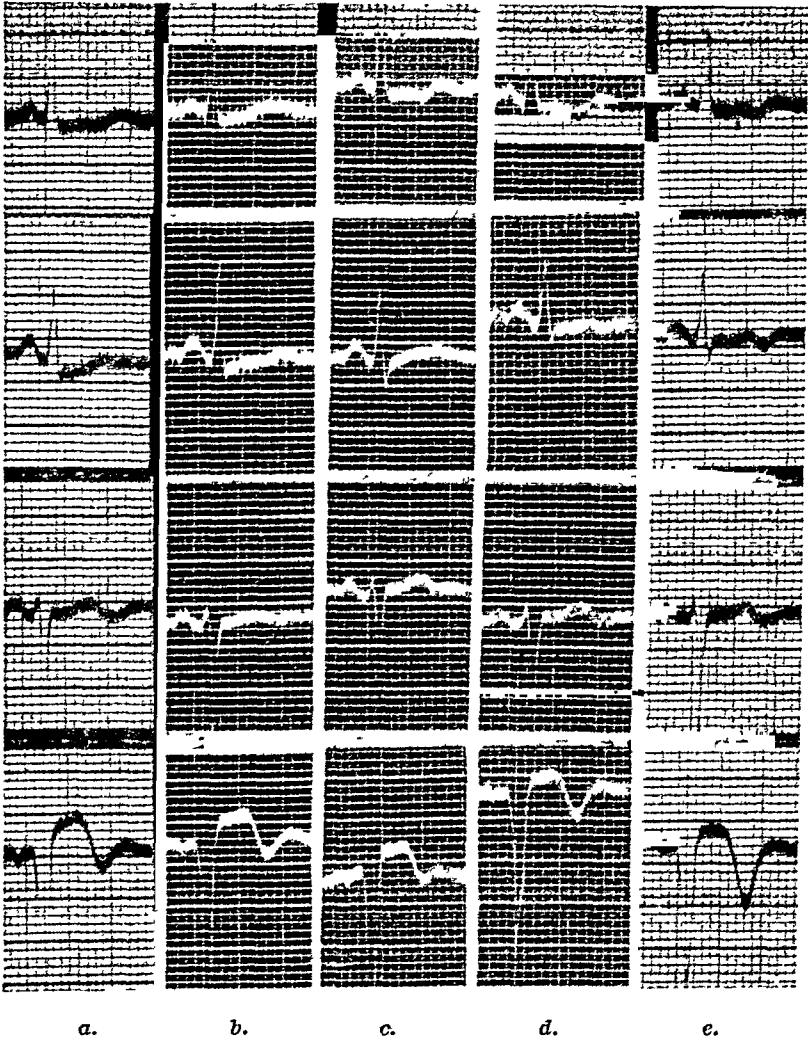


Fig. 6.—E.C., Jan. 2, 5, 8, 11, and 16, 1940. Attack Jan. 1, 1940. The diagnosis of recent anterior infarction could be suspected in the limb leads from the development of negative T waves in Leads I and II. In any single record, however, the diagnosis is made with certainty in Lead IVF only. No post-mortem examination.

a. Lead IV alone showed changes diagnostic of anterior infarction in one or more records in 29 cases (19 per cent). Of 34 cases examined post mortem, nine (26 per cent) showed definite diagnostic changes in Lead IV only. Further study of these cases is recorded in Table II.

TABLE II. ANTERIOR INFARCTION: CHARACTERISTIC CHANGES IN LEAD IV ONLY

DIAGNOSTIC CHANGES EVIDENT	NUMBER OF CASES	NUMBER CONFIRMED BY POST-MORTEM EXAMINATION
In only record made (Fig. 2)	4	1
In only 1 record of a series (Figs. 3 and 4)	7	2
In more than 1 record (usually initial 2 or 3 of a series of 6 or 8 records) (Fig. 5)	8	0
In all records of a series (Figs. 6 and 7)	10	6
Total	29	9

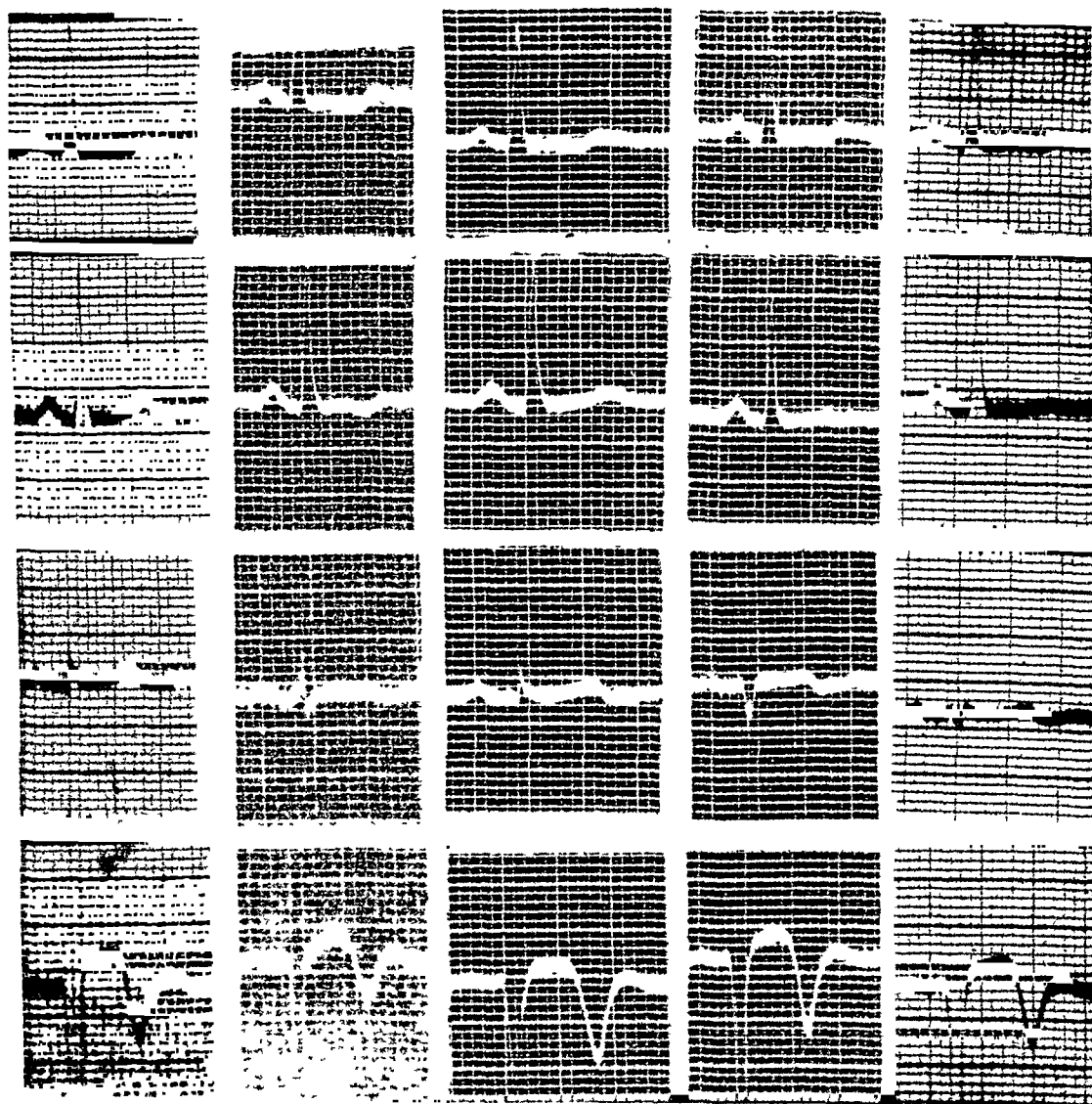


Fig. 7.—E.R., Aug. 22, 27, and 30, and Sept. 6 and 16, 1938. Attacks one year and two weeks prior to initial record. In spite of the marked change in T waves in the standard leads, Lead IVF alone contains certain evidence of anterior infarction.

b. The chest lead showed much more obvious and determinate evidence of recent anterior infarction than the minimal diagnostic changes in the limb leads in 35 (23 per cent) of the 152 cases. In the cases examined post mortem, eight (24 per cent) of the 34 cases fell into this group.

c. All four leads showed equally and simultaneously the changes of recent anterior infarction in 76 cases (50 per cent). Fifteen of these (44 per cent of the 34 cases examined post mortem) were proved anatomically.

d. In 12 cases (8 per cent) with diagnostic changes in the limb leads, Lead IV showed minimal, if any, changes (Table III). Two of these (6 per cent of the 34 cases examined post mortem) came to autopsy.

Since changes in the QRS complex in recent anterior infarction are more reliable diagnostically than T-wave changes alone, the initial deflection of the QRS complex has been examined in each case of recent anterior infarction (Table I). One hundred twenty-six cases (83 per cent) showed a negative

TABLE III. ANTERIOR INFARCTION: MINIMAL OR NO CHANGE IN LEAD IV

1. No change in Lead IV (Fig. 8)	4
2. T ₁ changes only—QRS not altered	8
a. T ₁ transiently low and notched (Fig. 9)	1
b. T ₁ slightly negative or diphasic	2
c. T ₁ deeply negative (Fig. 10)	5
Total number of cases	12

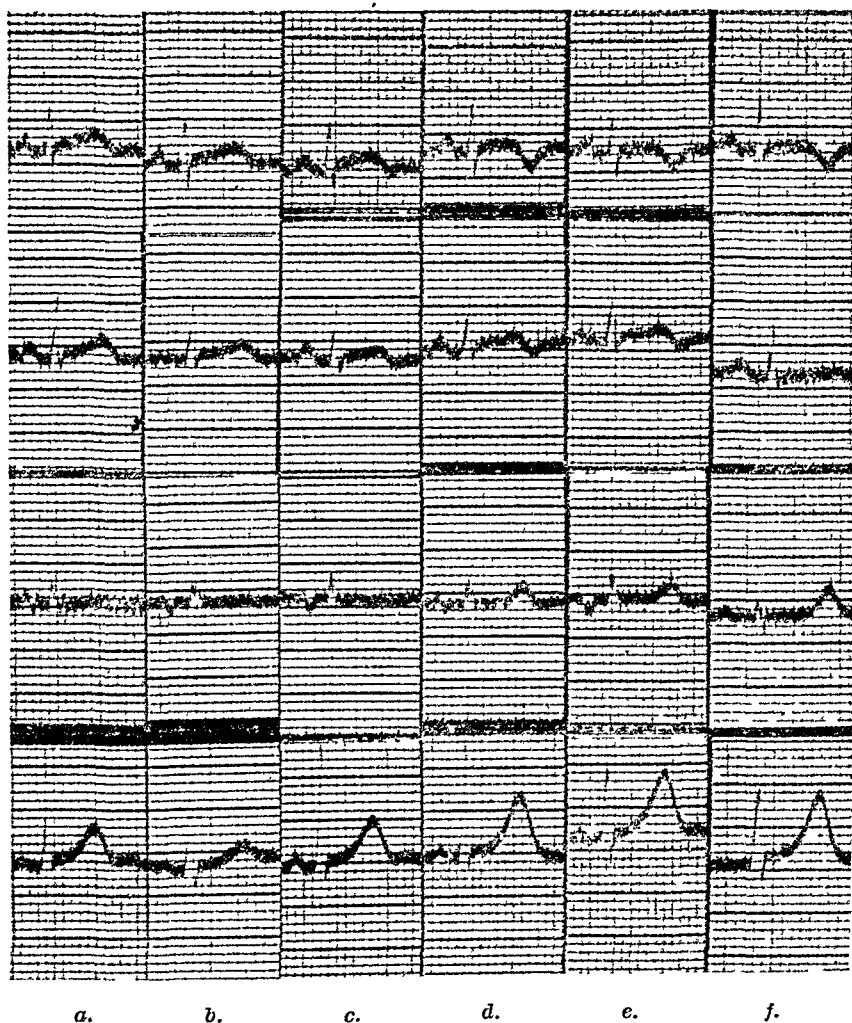


Fig. 8.—F.R., Jan. 20, 21, 23, 27, and 28, and Feb. 6, 1941. Attacks Jan. 14 and 16, 1941. While the limb leads were slow to change, the diagnosis of recent anterior infarction could not be made in Lead IVF which remained normal throughout the period of observation.

initial deflection; 11 cases (7 per cent) showed a positive initial deflection under 2 mm., i.e., a small R₄; the remaining 15 cases (10 per cent) showed a positive initial deflection greater than 2 millimeters.

Of the 34 cases which came to autopsy, 24 (70 per cent) showed an initial negative deflection of QRS₄; six cases (18 per cent) showed a small initial R₄; and four cases (12 per cent) had an initial R₄ greater than 2 mm. in height.

The majority of cases of recent anterior infarction presented an initial negative deflection of QRS_4 , with or without the disappearance of R_4 , in the first record which in many cases was made within a few hours of the attack.

Old Anterior Infarcts.—The results of analysis of 97 cases of "old" anterior infarction are found in Table IV. In 57 cases no record was obtained during the month after the acute attack. Fifteen of these were confirmed at autopsy. The remaining 40 of the 97 cases are tabulated as "follow-up" records; they represent cases included previously in the group of "recent" anterior infarcts, in which at least one record was obtained several months after the initial series.

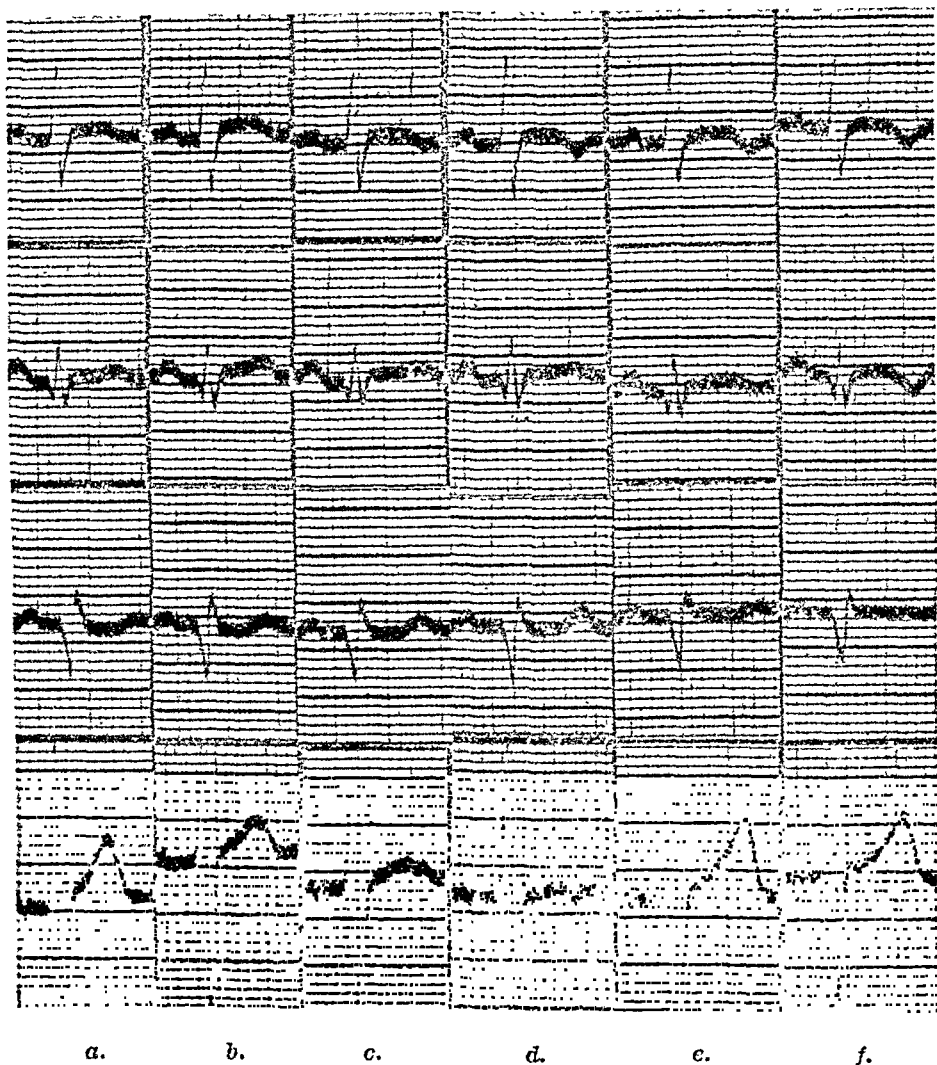


Fig. 9.—S.G., June 26, 27, 28, and 29, and July 3 and 14, 1939. Attack June 24, 1939. Diagnosis of recent anterior infarction can be made in the limb leads in the initial record, while Lead IVF is normal. While the T wave in Lead IVF becomes transiently low and notched in serial records, the diagnosis of anterior infarction is at no time possible from Lead IVF alone: R_4 remains normal in height throughout the series.

Lead IV showed the sole diagnostic evidence of anterior infarction in 46 cases (48 per cent) and much better and more certain evidence than Lead I in eight (8 per cent). The evidence was equally good in Leads I and IV in 36 cases (37 per cent). Lead I showed the only evidence in one case (1 per cent). In addition, there were six cases in the "follow-up" group which showed no residual electrocardiographic sign of the former attack.

An initial negative deflection of QRS_4 was found in 74 (76 per cent) of the 97 cases. An initial positive deflection under 2 mm. was present in 15 cases (16 per cent); while R_4 was over 2 mm. in eight cases (8 per cent).

It is interesting to scrutinize more closely the records of the follow-up group of 40 cases (Table V). These later records were all taken from six

TABLE IV. RELATIVE DIAGNOSTIC VALUE OF LEAD I AND LEAD IV IN NINETY-SEVEN CASES OF "OLD" ANTERIOR INFARCTION

DIAGNOSIS CONFIRMED BY	NUMBER OF CASES	INITIAL POSITIVE DEFLECTION, QRS ₄		
		ABSENT	SMALL	NORMAL
Lead IV only:				
Clinical diagnosis only	16	16	0	0
Examined post mortem	6	3	3	0
Follow-up	24	22	2	0
Total	46	41	5	0
Lead IV superior to Lead I:				
Clinical diagnosis only	7	7	0	0
Examined post mortem	1	0	1	0
Follow up	0	0	0	0
Total	8	7	1	0
Leads I and IV equal:				
Clinical diagnosis only	18	12	6	0
Examined post mortem	8	4	3	1
Follow-up	10	10	0	0
Total	36	26	9	1
Lead I only:				
Clinical diagnosis only	1	0	0	1
Examined post mortem	0	0	0	0
Follow-up	0	0	0	0
Total	1	0	0	1
Summary:	6	0	0	6
No remaining evidence (follow-up)				
Clinical diagnosis only	42	35	6	1
Examined post mortem	15	7	7	1
Follow-up	40	32	2	6
Total	97	74	15	8

months to two years after the patient was admitted to the hospital with the acute attack. In 24 cases Lead IV alone showed remaining evidence of the former anterior infarction; an initial negative deflection of QRS₄ only in 13 cases; an initial negative deflection of QRS₄ and a negative T₁ in nine cases; and a small initial positive deflection of QRS₄ in the remaining two cases, one of which also showed a negative T₄.

Leads I and IV were considered equally diagnostic of old anterior infarction in ten of these 40 cases. In eight of the ten, T₁ and T₄ were negative and coronary in shape, and were associated with an initial negative deflection in QRS₄. In the other two cases, T₄ had returned to a positive deflection.

TABLE V. "OLD" ANTERIOR INFARCTION: FOLLOW-UP RECORDS ON FORTY CASES

REMAINING DIAGNOSTIC EVIDENCE IN	NUMBER OF CASES
Lead IV only:	
Initial negative deflection of QRS ₄ only	13
Initial negative deflection of QRS ₄ and negative T ₁	9
R ₄ under 2 mm. only	1
R ₄ under 2 mm. and negative T ₄	1
	24
Leads I and IV equally:	
Initial negative deflection of QRS ₄	10
(T ₁ negative: T ₄ positive	2 cases
T ₁ and T ₄ negative	8 cases)
No residual evidence of former attack	6
Summary:	
T ₁ remained negative in 10 cases (25 per cent)	
T ₄ remained negative in 18 cases (45 per cent)	
QRS ₄ continued to show evidence of former attack in 34 cases (85 per cent)	

In the remaining six cases, complete reversion to normal had taken place.

Posterior Wall Infarction.—In recent posterior infarction the typical finding in Leads I and IV is temporary depression of the RT segments. A return to former levels is usually seen in the course of one to two weeks. In 57 (70 per cent) of a total of 82 cases, Leads I and IV showed these changes equally. Lead IVF was either the only lead to show RT depression or showed it much more obviously in 20 cases (24 per cent). Lead I alone showed this change in five cases (6 per cent).

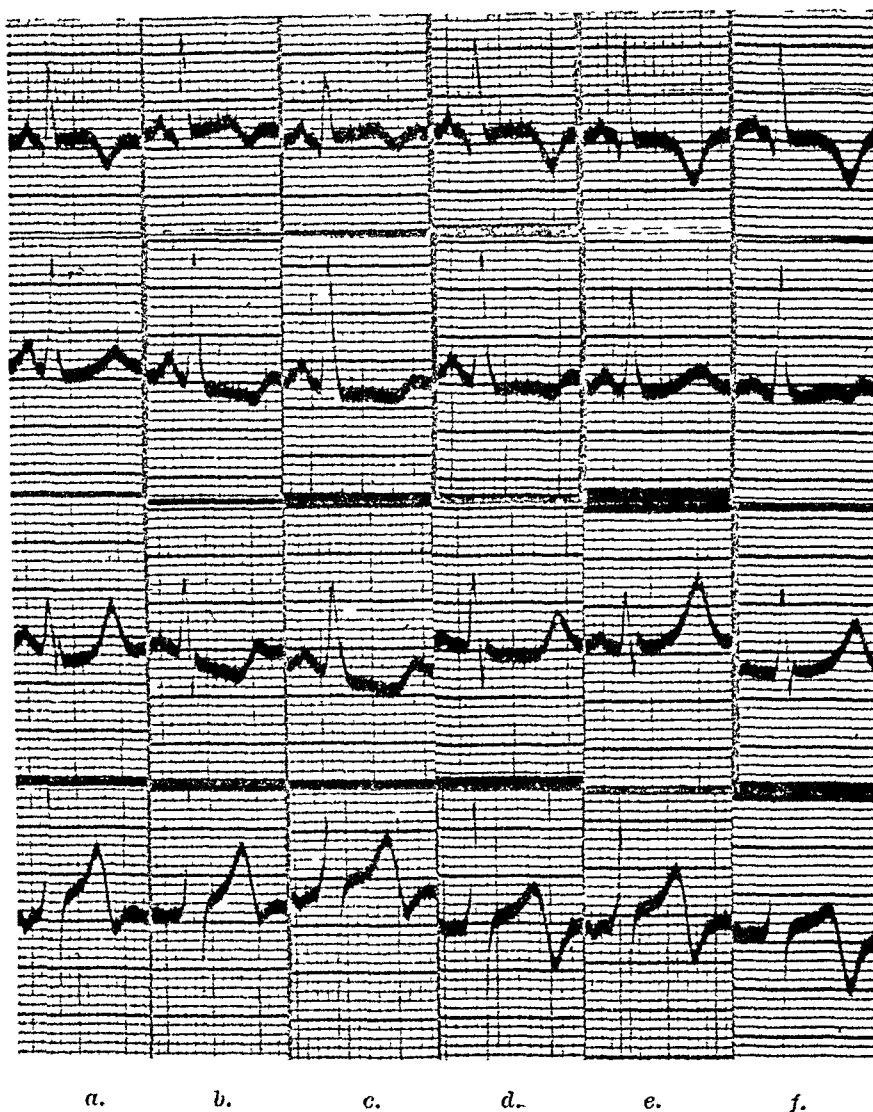


Fig. 10.—J.S., Aug. 13, 16, 19, and 22, and Sept. 9 and 16, 1941. Angina pectoris for three months. Prolonged pain Aug. 9, 1941. The diagnosis of anterior infarction is obvious in the limb leads. T wave in Lead IVF becomes progressively more negative; the R wave remains at normal height.

Neither Lead I nor IV showed any change which contributed to the diagnosis in old posterior wall infarction. There were 35 such cases.

Seven cases of recent posterior infarction and three cases of old posterior infarction came to autopsy. The electrocardiograms from these cases had shown R_s normal in height in seven and under 2 mm. in the other three cases; in none was it absent nor was there an initial negative deflection.

Multiple and Extensive Infarction.—Under this heading are considered those cases which in serial records do not fall readily into either the $T_1:T_4$ type (anterior) or the T_3 type (posterior). This group is composed of 47 cases which have been divided into three arbitrary groups.

1. Cases showing negative T waves in all four leads: There were 24 cases in this subdivision. Six came to autopsy (Table VI). In four of the six cases

TABLE VI. ELECTROCARDIOGRAPHIC CHANGES IN CASES OF MULTIPLE AND EXTENSIVE INFARCTION IN WHICH DIAGNOSIS WAS CONFIRMED AT AUTOPSY

	NO.
1. $T_1, 2, 3$, and 4 negative (6 cases):	
a. Infarction of anterior and posterior walls through septum: single attack, 1; multiple attacks, 3 (R_4 absent in 2 cases; R_4 small in 2 cases)	4
b. Infarction of anterior, lateral, and posterior walls (one attack, with R_4 absent, in both cases)	2
2. Lead IV behaved in manner opposite to that of limb leads (3 cases):	
a. Limb leads indicative of posterior infarction: Lead IV indicative of anterior infarction	2
i. Recent infarction of anterior and posterior walls of left ventricle and the adjacent anterior portion of septum—1 case	
ii. Old anterior and posterior infarcts plus small multiple pulmonary infarcts—1 case ($T_2, 3, 4$, negative; $Q_2, 3, 4$)	
b. Limb leads indicative of anterior infarction: Lead IV indicative of posterior infarction. Old and recent infarcts of anterior and posterior walls of the left ventricle and septum (R_4 normal)	1
3. Multiple infarction (1 case):	
Two infarcts—1 lateral and 1 posterior	1

examined post mortem, the infarct extended through the septum to involve both the anterior and posterior walls of the left ventricle. In the remaining two cases, the large infarct extended laterally around the left ventricle to lie both anteriorly and posteriorly. Ten of the 24 patients in this group suffered a single attack; 14 had more than one attack. The initial deflection of QRS_4 was negative in 15 of the 24 cases; positive but small in three; and normal in height in six cases.

2. Cases in which Lead IV behaved in the opposite manner to changes in the limb leads: Twelve cases fell into this group. In eight of these Lead IV showed changes either typical or very suggestive of anterior infarction, while limb lead changes alone indicated posterior wall localization. In the other four cases the reverse was true: limb leads suggested anterior infarction, while Lead IV indicated posterior wall involvement.

Three of the 12 cases came to autopsy. One, in which Lead IV suggested anterior infarction while the limb leads suggested posterior infarction, showed recent infarction of anterior and posterior portions of the left ventricle and of the anterior (adjacent) portion of the interventricular septum. In another case with the same electrocardiographic findings, old anterior and posterior cardiac infarcts were demonstrated along with small multiple pulmonary infarcts. The electrocardiographic findings of negative T waves in Leads II, III, and IV, together with $Q_2, 3, 4$, are thus accounted for. The remaining case in which the limb leads, in a single record taken just before death, suggested anterior infarction and Lead IV posterior infarction, showed old and recent infarcts of the anterior and posterior walls of the left ventricle and septum.

3. Cases of multiple infarction under clinical observation throughout the course of more than one attack of cardiac infarction: In each of the 11 cases in this group electrocardiographic changes gave adequate evidence of two or more separate clinical episodes diagnosed cardiac infarction. It is interesting to note that in two of five cases with evidence of an older anterior infarct upon which had been superimposed a recent posterior infarct the well-marked initial negative deflection of QRS_4 , that developed as the result of the anterior infarction, completely disappeared leaving a normal R_4 (initial positive deflection) with the advent of the posterior infarct.

Atypical Infarcts.—There were 15 cases with history suggestive of recent coronary occlusion in which there was evidence of cardiac infarction, such as transient fever and leucocytosis, but in which serial electrocardiographic records failed to show diagnostic changes. None of these cases came to autopsy.

Coronary Occlusion Without Infarction.—In 18 cases in which the history suggested recent coronary occlusion, the clinical course was not characterized by fever and leucocytosis. Electrocardiograms in these cases commonly showed T-wave changes, usually without changes in the QRS. These could not be considered cases of cardiac infarction. In the majority, T_4 became transiently negative. Three of the 18 cases in this group came to autopsy. It is of interest that one case with recent thrombosis of the anterior descending branch of the left coronary artery without visible infarction in the ventricle had shown a definite initial negative deflection of QRS_4 (Q_4).

SPECIAL STUDY OF 165 CASES EXAMINED POST MORTEM

In order to visualize more clearly the significance of the change which usually occurs in the QRS complex of Lead IVF with the advent of anterior infarction, 165 cases examined post mortem were selected for special study. Of these, 58 cases showed anterior wall infarction, and 107 showed other forms of heart disease. A striking contrast is thus presented by these two groups with respect to the initial deflection of the QRS complex (Table VII).

TABLE VII. ELECTROCARDIOGRAPHIC FINDINGS IN FIFTY-EIGHT CASES OF ANTERIOR INFARCTION AND 107 CASES OF OTHER FORMS OF HEART DISEASE EXAMINED POST MORTEM

CLINICAL DIAGNOSIS	NUMBER OF CASES	INITIAL POSITIVE DEFLECTION, QRS_4		
		ABSENT	SMALL	NORMAL
Anterior infarcts (in four-year period):				
Recent	35	25	6	4
Old	14	6	7	1
Complicated	9	6	1	2
Total	58 (100%)	37 (64%)	14 (24%)	7 (12%)
Infarction other than anterior (in four-year period)	11	0	4	7
Coronary occlusion without infarction (in four-year period)	3	1	0	2
Other forms of heart disease (in thirty-month period)	93	6	19	68
Total	107 (100%)	7 (6.5%)	23 (21.5%)	77 (72%)

The chief cardiac changes of significance, in relation to QRS_4 , found at autopsy in the 165 cases selected for special investigation were as follows:

$Q_4 R_4$ (nine cases):

Anterior infarcts were found in	7 cases
Recent thrombosis of the anterior descending branch of the left coronary artery was found in	1 case
Pulmonary embolism but no cardiac infarction was found in (Q_4 was present in only one of four serial records on this case)	1 case

R_4 absent (35 cases):

Anterior infarction was found in	30 cases
Pulmonary embolism was found in	3 cases
Pericarditis was found in	1 case
Aortic valvular disease with left ventricular hypertrophy was found in	1 case

R_4 small (2 mm. or less) (37 cases):

Anterior infarction (left bundle branch block in 2 cases) was found in	14 cases
Left ventricular hypertrophy curve (result of hypertensive cardiovascular disease or aortic valvular disease) was found in	12 cases
Lateral wall infarction was found in	4 cases
Posterior infarction together with coronary sinus thrombosis was found in	1 case
Syphilitic aortitis with posterior infarction was found in	1 case
Periarteritis nodosa of coronary arteries was found in	1 case
Pulmonary heart disease was found in	1 case
Miscellaneous lesions (left bundle branch block in 1 case) were found in	3 cases

R_4 normal height (over 2 mm.) (84 cases):

Anterior infarction (in 2 cases, Lead IV suggested posterior infarction) was found in	7 cases
Posterior infarction was found in	8 cases
Recent coronary thrombosis without infarction was found in	2 cases
Left ventricular hypertrophy curve was found in	28 cases
Miscellaneous forms of heart disease other than above were found in	39 cases

Other investigators^{12, 16, 18, 21, 22, 23} have pointed out that changes in QRS_4 are more reliable diagnostic evidence of anterior infarction than T_4 changes alone. This observation has been confirmed in this series of cases by a negative T_4 associated with the following conditions: (1) left ventricular hypertrophy, a result of hypertensive cardiovascular disease or aortic valvular disease; (2) pulmonary embolism; (3) pericarditis; (4) a few cases of arteriosclerotic heart disease without infarction and without a left ventricular hypertrophy curve; (5) certain adults apparently without heart disease, including some adolescents in whom the clinical diagnosis was "neurasthenia"²⁴; (6) following an arrhythmia such as paroxysmal auricular tachycardia, paroxysmal flutter or fibrillation (transiently negative T_4 in serial records); (7) nephritis, acute and chronic; (8) myxedema; (9) Addison's disease; (10) congenital heart disease; and (11) digitalis effect. There are no records on children in this series.

DISCUSSION

With such a large variety of conditions giving rise to a negative T wave in Lead IVF, it is fortunate that with the advent of anterior infarction changes occur as described above, e.g., the appearance of an initial negative deflection of the QRS (Q wave) with coincident reduction or absence of the positive deflection (R wave). The significance of the presence of a Q wave in Lead IVF has received extensive study. Master and associates²¹ found that 88 per cent of 120 cases exhibiting a Q_4 were probably anterior infarcts. Vander Veer and Edwards²² report that 67 per cent of 102 cases of absent R_4 had anterior infarction. Cutts, Clagett, and Fulton,²³ in a group of 30 cases with similar electrocardiographic findings which were examined post mortem, found evidence of anterior infarction in 87 per cent.

In Table VII it is shown that, of the 58 cases of anterior infarction examined post mortem in the present series, 64 per cent showed an initial negative deflection, which is in sharp contrast to 6.5 per cent of 107 cases of other forms of heart disease. Conversely, an initial positive deflection (R) in excess of 2 mm. was found in 72 per cent of other forms of heart disease, while only 12 per cent of anterior infarction cases presented a normal R_4 .

Since the series of cases of infarction extended over a longer period (48 months) than the series of other forms of heart disease (thirty months), consideration of the 44 cases presenting an initial negative deflection of QRS₄ could not be reduced to percentage of those showing anterior infarction without weighting the figures. With proper weighting, 77 per cent of cases with an initial negative deflection showed anterior infarction; of the cases with a normal positive initial deflection, 5.6 per cent had anterior infarction.

Difficulty may be encountered in the correct interpretation of an initial positive deflection (R₄) less than 2 mm. in height. Levine and Levine²⁵ state that 50 per cent of cases of angina pectoris showing small initial positive deflection of QRS₄ have had anterior infarction. After weighting, 29 per cent of all cases in this series with an initial positive deflection less than 2 mm. in height showed anterior infarction at post-mortem examination.

Value of Lead IV in Anterior Infarction.—Recent infarction: As noted above, 29 (19 per cent) of 152 cases of anterior infarction showed diagnostic changes in Lead IVF alone in at least one record of a series done on an individual case. These may be subdivided as follows:

1. In 14 cases (9 per cent) diagnostic changes were entirely lacking in the limb leads: in serial records on ten cases (6 per cent); and in the only record obtained on four cases (3 per cent). The usual cause of failure of the limb leads to show certain evidence of anterior infarction was pre-existing electrocardiographic abnormality, such as a left ventricular hypertrophy curve.

2. In 15 cases (10 per cent) the electrocardiographic diagnosis was established by Lead IVF hours or days in advance of the appearance of diagnostic changes in the limb leads.

In addition, there were 35 cases (23 per cent) of recent anterior infarction in which the chest lead showed much more obvious and definite diagnostic changes than the minimal changes in the limb leads. Thus in 42 per cent of 152 cases Lead IVF was either of considerable or of paramount importance to the electrocardiographic diagnosis.

When the series of 34 cases examined post mortem is segregated, Lead IVF is seen to have an even greater value. In 26 per cent of these cases Lead IV alone revealed the diagnosis, while it had a marked advantage over the limb leads in contributing to the correct diagnosis in a further 24 per cent. Thus, in half the proved cases of anterior infarction Lead IVF provided more definite diagnostic evidence than the limb leads.

These findings are in agreement with those of other investigators. Goldbloom⁴ found that Lead IV alone showed diagnostic changes in 7.5 per cent of cases of coronary occlusion. Bohning and Katz²⁶ state that, as a rule, infarction is more easily diagnosed early from Lead IV. Willcox and Lovibond²⁷ found that 35 per cent of 20 cases showed the only significant electrocardiographic changes in Lead IV soon after the attack, while the same was true in 20 per cent of their series of 20 cases in which the infarcts were slightly older. Lieberman and Goldbloom²⁸ summarized their report of seven years' experience with chest leads by stating that Lead IV "increases the efficiency of the conventional leads in detecting and corroborating evidence of acute coronary thrombosis in about 10 per cent of the cases if serial (and occasionally multiple) precordial leads are used; by about 4 or 5 per cent when single four-lead electrocardiograms are used."

Old infarction: Lead IV had a still greater advantage over the limb leads in the diagnosis of old anterior infarction.^{2, 28, 29} Lead IV provided the sole diagnostic evidence in 46 (48 per cent) of the 97 cases, while in a further 8 per cent the evidence was much better in Lead IV than in the limb leads.

Attention has been directed to the persistence of the altered QRS_4 as the result of anterior infarction.^{12, 16, 21, 22} In the present series of cases, the frequency with which QRS_4 alone showed remaining diagnostic evidence of the former attack has been noted, T_4 having reverted to an upright deflection in the majority of cases.

Atypical infarction: Following acute occlusion of a large branch of one of the coronary arteries, the size and extent of infarction of the myocardium depend largely on the degree of atherosclerotic narrowing present in the remainder of the branches of the coronary tree. Thus, it is not surprising that the electrocardiographic tracing frequently does not conform to the typical anterior or posterior pattern. As noted in the review of cases of atypical infarction, Lead IVF may definitely increase the value of the electrocardiogram in localizing the infarct by behaving in a manner opposite to that of the limb leads.

SUMMARY AND CONCLUSIONS

1. Analysis of the electrocardiographic records of cases of cardiac infarction admitted to the public ward of the Toronto General Hospital during a four-year period has been made. The records consist of the standard limb leads and Lead IVF.

2. Study was also made of the electrocardiographic records of all cases showing abnormality in the ventricular complex ($QRS-T$), admitted during the first thirty months of the same four-year period. However, only the records of those cases coming to autopsy were analyzed for comparison with the proved cases of cardiac infarction.

3. Lead IVF was found to present the sole diagnostic evidence of recent anterior infarction in 19 per cent of 152 cases, and in 48 per cent of 97 cases of old anterior infarction.

4. Lead IVF presented the main diagnostic evidence in a further 23 per cent of cases of recent anterior infarction, and in a further 8 per cent of old anterior infarction.

5. Thus, Lead IVF had a definite advantage over the limb leads in contributing to the electrocardiographic diagnosis in 42 per cent of recent and in 56 per cent of old anterior infarction cases.

6. In 47 cases of infarction showing changes other than the typical anterior or posterior distribution, Lead IVF was important to the electrocardiographic localization of the infarct by behaving in a manner opposite to the changes in the limb leads in 12 cases (25 per cent).

7. Changes in QRS_{4F} in anterior infarction were described in detail and their outstanding characteristics compared with the QRS_4 findings in anatomically proved cases of other forms of heart disease, including infarction other than anterior.

8. The conditions other than anterior infarction associated with inversion of T_4 have been enumerated. The electrocardiographic diagnosis of anterior infarction was much more reliable when the ventricular complex as a whole in Lead IVF underwent characteristic changes.

9. Of the cases examined post mortem, in which an initial negative QRS_4 deflection had been recorded, 77 per cent showed anterior infarction.

10. Approximately 29 per cent of cases examined post mortem, which had presented an initial positive deflection less than 2 mm. in height, showed anterior infarction.

11. Of the cases with a normal initial positive QRS_4 deflection which came to autopsy, 5.6 per cent showed anterior infarction.

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OBSERVATIONS ON TWO PATIENTS WITH PAROXYSMAL
VENTRICULAR TACHYCARDIA TREATED BY THE
INTRAVENOUS ADMINISTRATION OF
QUINIDINE LACTATE

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PAROXYSMAL ventricular tachycardia¹ is generally, but not always, associated with grave heart disease. In most instances it is associated with disease of the coronary arteries, occurring in 5 per cent of all myocardial infarctions. Ventricular tachycardia is not always fatal when it occurs with coronary occlusion. It may be transient lasting for only a few hours and causing no particular problem in treatment; on the other hand, it may be persistent and resistant to therapy and may terminate fatally. It has occasionally been witnessed following the administration of digitalis² and has also been precipitated by slight physical exertion³ in individuals without other clinical evidence of heart disease. Experimentally it has occurred in cats following the administration of low tension chloroform vapor,⁴ and Robinson and Herrmann⁵ found it frequently in dogs following ligation of the coronary arteries. The purpose of this paper is to present some of the aspects in diagnosis and treatment of ventricular tachycardia, including the report of two unusual cases treated by the intravenous administration of quinidine lactate.

CASE REPORTS

CASE 1.—W. C. This patient was admitted to the University Hospitals on Oct. 14, 1942. Two days previously, he had experienced a typical attack of coronary occlusion with precordial pain radiating to both shoulders and up the back of his neck. The sharp pain had been replaced by a dull precordial distress and was accompanied by nausea and vomiting.

Physical examination on admission, revealed a rather obese 52-year-old, acutely ill, orthopneic, disoriented, cyanotic white man with a flushed facies. The pupils were contracted (due to the administration of morphine), and the tongue was dry. The left border of the heart was 2 cm. to the left of the midclavicular line. The heart tones were distant and a variable friction rub was present all over the precordium. The heart rate was approximately 200 beats per minute, but the rhythm was regular. The systolic arterial pressure was 90 and the diastolic was 80 mm. of mercury. The lungs contained a few moist râles at the bases. No other significant physical findings were present.

An electrocardiographic tracing was taken immediately after admission, which revealed ventricular tachycardia at a rate of 210 beats per minute (Fig. 1). At 7:45 P.M., approximately thirty minutes after admission, quinidine lactate, in a dosage of 0.65 Gm., was administered intravenously. An electrocardiographic tracing taken seven minutes later revealed a normal mechanism with a rate of 90 beats per minute. The patient then received, orally, 0.2 Gm. (3 grains) of quinidine sulfate, 30 mg. ($\frac{1}{2}$ grain) of papaverine hydrochloride, and 0.2 Gm. (3 grains) of theophylline ethylenediamine four times daily, and, in addition intranasal oxygen.

During his hospital stay, from Oct. 14, 1942, to June 12, 1943, the patient had six more attacks of ventricular tachycardia, all proved by electrocardiographic tracings. Each attack was successfully stopped by the intravenous administration of quinidine lactate in doses varying from 0.325 Gm. to 1.3 Gm. During the fifth attack, during which 0.65 Gm. of quini-

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dine lactate was injected intravenously without effect and 0.26 Gm. was repeated thirty minutes later, the patient's heart tones suddenly stopped, he had a generalized convulsion, and approximately three to five seconds later he vomited, his heart tones became audible, and the cardiac mechanism had returned to normal. During the first five months of hospitalization, he received quinidine sulfate orally in doses varying from a minimum of 3 grains four times per day to 5 grains six times per day. He was maintained, during the last three months of his hospital stay, without recurrence of his attacks on a total oral dose of 30 grains of quinidine sulfate per day.

Following discharge from the hospital, he took quinidine rather spasmodically and finally discontinued it. On July 17, 1943, he apparently had another episode of coronary occlusion with severe precordial pain radiating into both arms. After this the symptoms recurred similar to those previously experienced during the attacks of tachycardia.

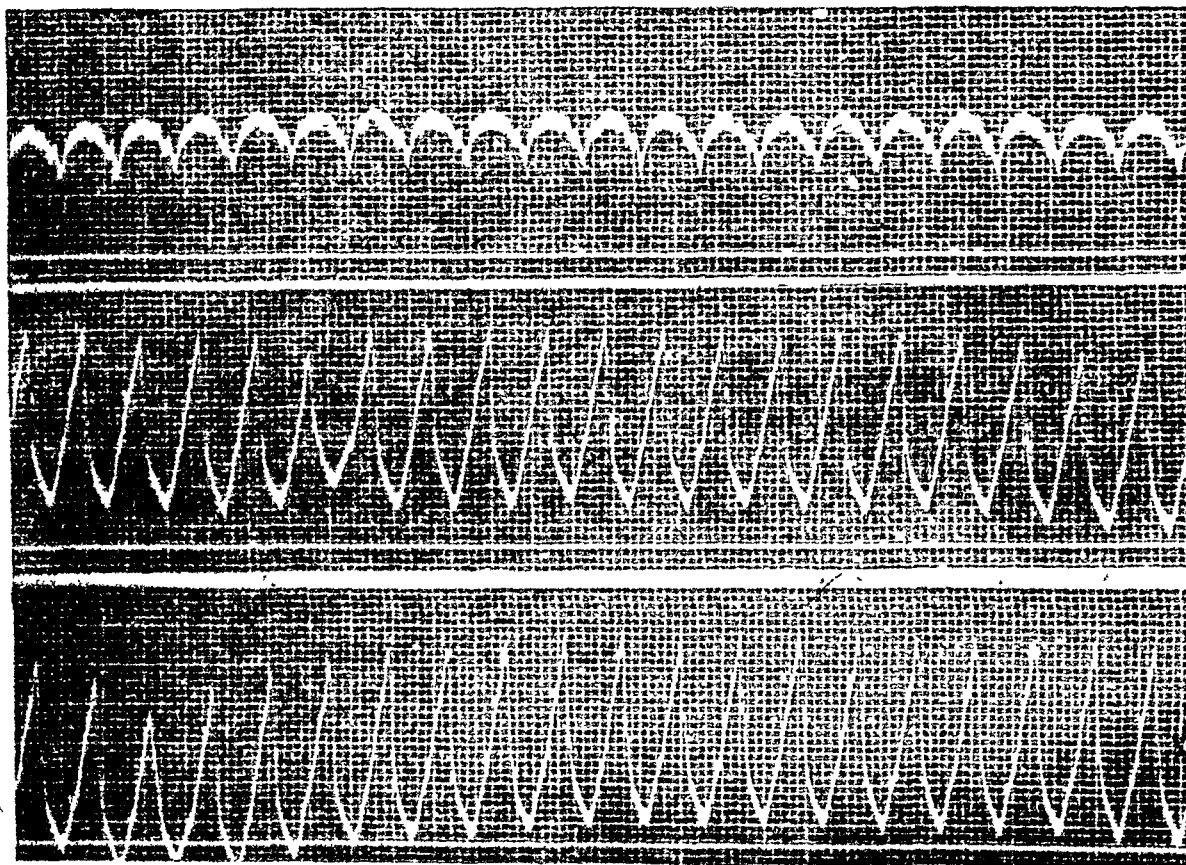


Fig. 1.—Electrocardiographic tracing of paroxysmal ventricular tachycardia.

He returned to the hospital on Oct. 10, 1943, for five weeks during which time he was maintained on a dose of 30 grains of quinidine sulfate orally without recurrence of the tachycardia. An electrocardiographic tracing (Fig. 2), obtained on this admission, revealed evidence of a fairly recent anterior coronary infarction. On Nov. 19, 1943, he was again admitted during an attack of ventricular tachycardia which was successfully converted to a normal mechanism by the intravenous administration of quinidine lactate in divided doses of 0.65 Gm. each. He remained in the hospital three months during this visit and received 30 grains of quinidine sulfate orally daily without further attacks.

The patient has continued to take quinidine sulfate faithfully and when last seen, May 25, 1944, he had had no further attacks of tachycardia. An electrocardiographic tracing taken at that time was essentially normal except for an occasional premature ventricular contraction.

CASE 2.—B. H. This patient was admitted to the University Hospitals on Feb. 16, 1944. In the summer of 1937, this 47-year-old white man, while lifting a barrel, suddenly experienced a severe, vicelike pain in the substernal region. He fell to the ground but did not lose consciousness. Soon afterwards the pain disappeared and he felt all right. In the summer of 1938, he again suddenly fell to the ground without previous pain or other warning. He was not unconscious nor did he lose control of his bowel or bladder. There was no precordial distress connected with this episode. The patient was put to bed for two weeks and was given twenty drops of digitalis daily, which was soon discontinued. During the five years preceding his first admission to the University Hospitals, he had had repeated "heart attacks." These

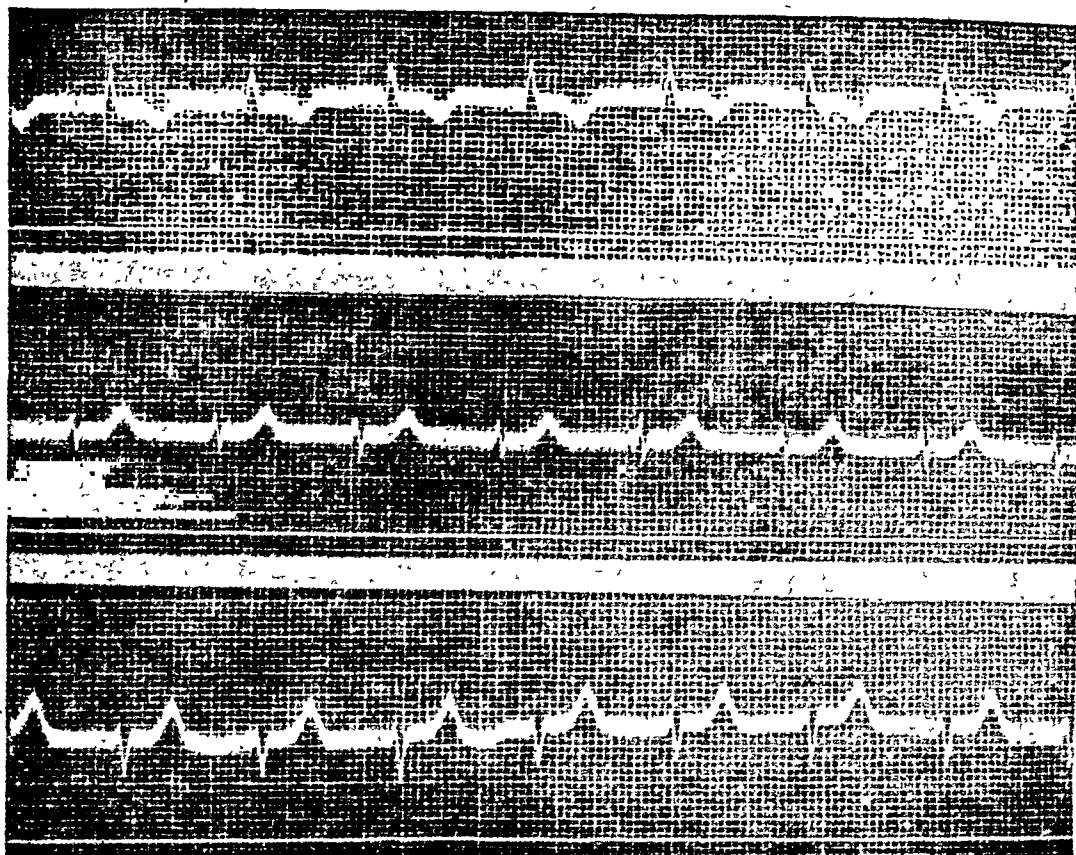


Fig. 2.—Electrocardiographic tracing of nodal rhythm in evidence of a fairly recent anterior myocardial infarction.

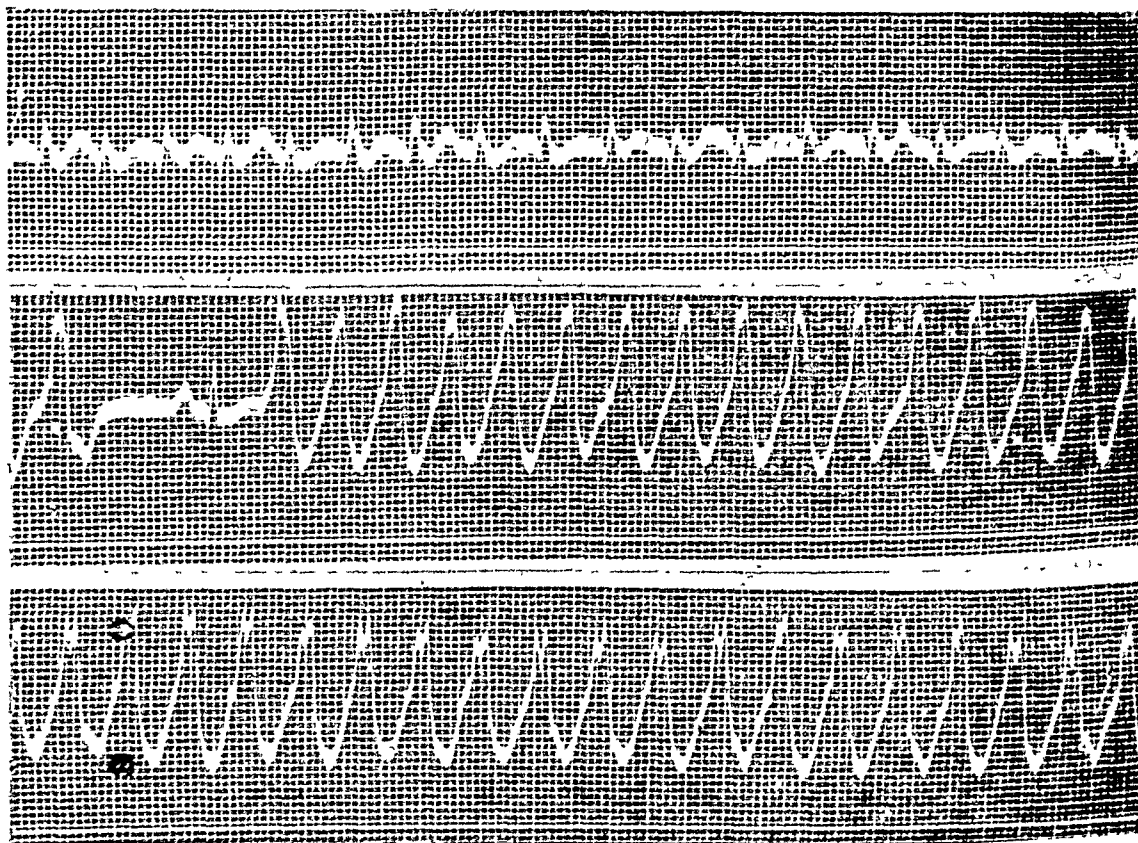


Fig. 3.—Electrocardiographic tracing of paroxysmal ventricular tachycardia with one cycle of normal mechanism in Lead II.

attacks were usually rather sudden in their onset with a rapid, "fluttery" feeling in the heart. Accompanying these attacks, there would be rather severe substernal pain which would radiate to the right shoulder and down the inner aspect of the right arm as far as the wrist. The attacks usually terminated quite suddenly, although sometimes the offset was gradual. The physician who originally saw this patient gave him quinidine sulfate in doses up to 27 grains daily, without effect, so that the medication was discontinued. The final month before his hospital admission, he had experienced considerable exertional shortness of breath, but no orthopnea, dyspnea, or ankle edema.

Physical examination revealed a moderately obese, ambulatory, 47-year-old white man without cyanosis or ankle edema. The heart was not enlarged, the rhythm was regular, and the rate was 76 beats per minute. The heart tones had a somewhat mushy quality but no definite murmurs were present. The systolic arterial pressure was 140 and the diastolic was 95 mm. of mercury. Dullness was elicited in the left lung base with some diminution in the breath sounds. No other significant physical findings were observed.

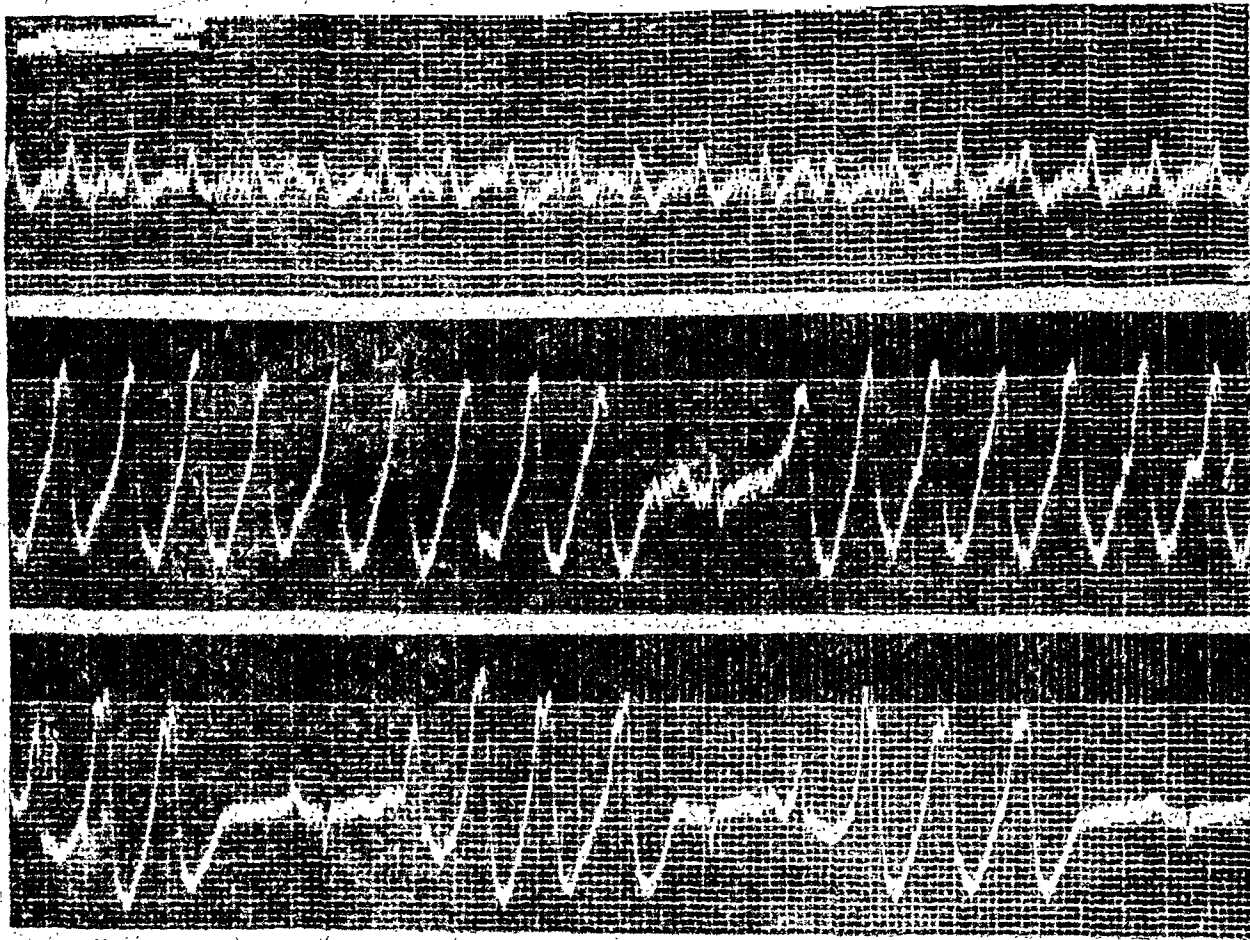


Fig. 4.—Electrocardiographic tracing of paroxysmal ventricular tachycardia with cycles of normal mechanism appearing in Leads II and III five minutes after the intravenous administration of 0.65 Gm. of quinidine lactate.

A teleroentgenogram revealed a thickening of the pleura at the left base of the lungs without cardiac enlargement. An electrocardiographic tracing taken on Feb. 16, 1944, was normal. Urinalyses and blood examinations were negative. Blood Kolmer and Kline tests were negative.

Attempts to reproduce an attack by exercise were unsuccessful. That same evening, however, the patient spontaneously developed a tachycardia with flushing of his face, mild apprehension, and rather profuse diaphoresis, but no precordial distress. An electrocardiographic tracing obtained at that time revealed ventricular tachycardia (Fig. 3). Carotid pressure failed to alter the tachycardia, and quinidine lactate in 0.65-Gm. doses administered intravenously also failed to convert it to a normal mechanism. An electrocardiographic tracing taken five minutes later (Fig. 4) showed slight alteration from the previous one. Fifteen minutes later an electrocardiographic tracing revealed the presence of auricular tachycardia with several premature ventricular beats (Fig. 5).

The patient was then placed on 3.6 Gm. (54 grains) of quinidine sulfate orally daily in divided doses. Despite its constant administration, he continued to have attacks of tachycardia, and on all subsequent electrocardiographic tracings, five in all, the attacks were ventricular in origin. The attacks lasted from twenty minutes to forty-eight hours regardless of whether or not he was receiving quinidine. Unfortunately, it was necessary for the patient to go home due to outside circumstances. Quinidine therapy was discontinued, and he was discharged on March 10, 1944, with instructions to return in one month.

While at home, he stated he had had an attack lasting from March 11 to March 16, 1944, with the symptoms described previously. Following this he had several attacks lasting from one hour to three days. For the six days prior to readmission on March 30, 1944, he had experienced no attacks.

On April 4, 1944, while in the hospital, he had another attack. Electrocardiographic tracings revealed typical ventricular tachycardia. Since the patient had not previously responded to quinidine, and because there was a possibility that the origin of the tachycardia was a circus movement about the base of the aorta, perhaps giving a ventricular type of electrocardiographic tracing, it was felt that the tachycardia might respond to supra ventricular medication. Therefore mecholyl (acetyl-beta-methyl-choline) was given in the usual dosages without effect. Then 0.6 mg. of lanatoside C were administered intravenously, and within fifteen minutes his cardiac mechanism was restored to normal without any preliminary slowing. Again the patient insisted on going home, therefore we have no further studies as to the effectiveness of lanatoside C.

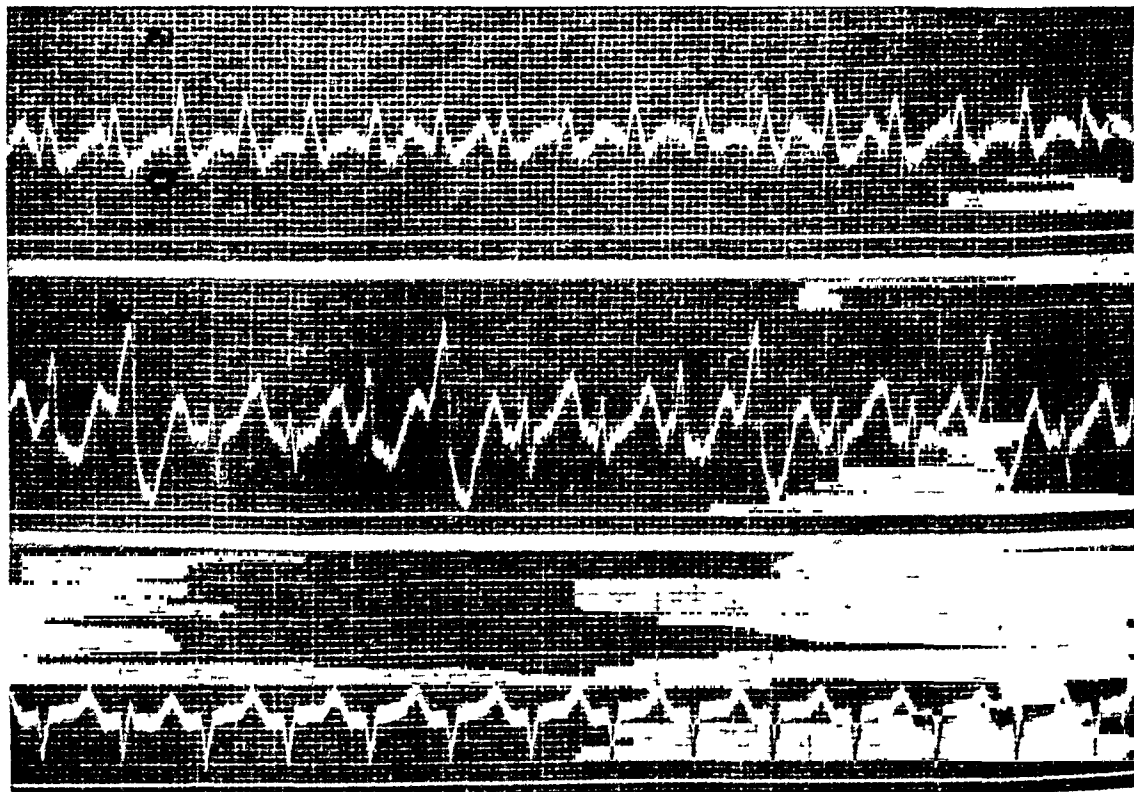


FIG. 5.—Electrocardiographic tracing of paroxysmal auricular tachycardia with premature beats of the ventricle in Lead II, fifteen minutes after the intravenous administration of 0.65 Gm. of quinidine lactate.

DISCUSSION

Ventricular tachycardia may sometimes be anticipated in the earlier days or weeks following a coronary occlusion by the development of multiple ventricular premature beats or by periods of excessively rapid heart beats. In Case 1, whenever the patient began to develop an excessive number of premature beats usually an attack of ventricular tachycardia soon developed.

In ventricular tachycardia, the auricles beat independently of the ventricles but at a slower rate. According to Grieco and Schwartz⁸ the rapid

beating of the ventricles may progressively augment the ventricular pacemaker, and thus lead ultimately to asystole. Theoretically, therefore, the cause of death in patients with ventricular tachycardia should be ventricular asystole rather than ventricular fibrillation, and such a mechanism has been found in about one-half of the cases studied at the time of death.⁷

Levine⁸ states that it is clinically possible to distinguish ventricular tachycardia from other forms of rapid heart action by the following three points: first, the rhythm is rapid and is essentially regular but slight irregularities can be detected; second, the quality of the first heart sound varies in some of the cycles; third, attempts at vagal or ocular pressure prove ineffective in slowing the tachycardia. Final positive evidence of ventricular tachycardia, however, requires electrocardiographic studies. In our second case (Fig. 5), one episode of tachycardia was auricular in origin; however, the subjective manifestations were no different than in those attacks of ventricular tachycardia. The first electrocardiographic tracings on a case of ventricular tachycardia followed by ventricular fibrillation occurred in an 80-year-old woman and was reported by Reid.⁹ Paroxysms of ventricular tachycardia are believed to originate either in the bundle branch tissue or in the muscle of the ventricle. They are characterized, according to Pardee,¹⁰ by typical wide, notched QRS complexes followed by T waves directed opposite to the chief deflection of the QRS group. The P waves may be entirely lost in the large excursions of the ventricular waves, as in our tracings, or the P waves may be discerned occurring in a slower independent rhythm.

The intravenous administration of quinidine lactate is not going to be applicable universally in the treatment of ventricular tachycardia. Our first case, a 52-year-old white man, who had at least two and possibly three attacks of coronary occlusion, experienced eight attacks of ventricular tachycardia proved by electrocardiographic tracings, and each of them was successfully treated with the intravenous administration of quinidine lactate. In the second case, on the other hand, the intravenous administration of quinidine lactate failed to stop any of this patient's attacks of paroxysmal ventricular tachycardia. The tachycardia responded to the intravenous administration of lanatoside C on one occasion, but further studies were not obtained because the patient left the hospital. Prophylactically, the recurrence of the attacks was prevented in the first patient by the oral administration of 30 grains of quinidine sulfate daily. In the second case, on the other hand, recurrences of the attacks continued even with the oral administration of 54 grains of quinidine sulfate daily.

According to Goodman and Gilman,¹¹ quinidine acts on the heart by increasing the absolute refractory period often as much as 50 to 100 per cent, decreasing the myocardial excitability, and slowing the conduction of impulses in the heart muscle. Drury, Horsfall, and Munly¹² found that quinidine has the same effect on ventricular muscle that it has on the muscles of the auricle. In Levy and Lewis^{13, 14} experiments on cats, it was found that quinidine raised the threshold current for ventricular fibrillation; likewise, the same results were obtained on dogs by Drury, Horsfall, and Munly.¹² Levine and Fulton¹⁵ believe that quinidine not only breaks up the abnormal rhythm but may prevent its return when the condition has a tendency to recur in paroxysms.

Toxic¹¹ reactions to quinidine are fairly common. Everyone is familiar with cinchonism and its accompanying gastroenteric symptoms, tinnitus, and impaired vision. Idiosyncrasies to the drug in the form of respiratory dis-

tress (occasionally with temporary cessation of respiration), cyanosis, dizziness, nausea, vomiting, and cold sweats occur. The various embolic phenomena that occur with a sudden reversion to a normal mechanism after months of auricular fibrillation, serves as a contraindication to its usage in that condition, but not so to its administration in ventricular tachycardia. Occasionally ventricular standstill, due to the depressant action on the sinoauricular or auriculoventricular nodes, is encountered, and this may be fatal. Death from ventricular fibrillation after quinidine occurs more commonly than is stated.¹¹

The administration of quinidine in anticipation of the development of an attack of ventricular tachycardia may prevent it. Scott,³ in 1922, first demonstrated this effect of quinidine in preventing as well as stopping paroxysms of ventricular tachycardia. His patient was a 39-year-old woman without evidence of organic heart disease. Initially, her attacks were stopped on 0.4 Gm. of quinidine sulfate administered orally three times daily; later she was maintained on 0.2 Gm. daily without recurrence of the attacks. He had also tried digitalis, epinephrine, and glyceryl trinitrate without success in stopping the tachycardia.

Quinidine has been used prophylactically in the prevention of paroxysmal ventricular tachycardia as well as in the treatment of it. Test doses of 3 grains of quinidine sulfate should be given, and during the ensuing twenty-four hours the individual should be observed for any untoward reactions, especially those occurring with idiosyncrasy reactions. If these occur, the drug should not be employed. If no reactions occur, however, it is probably safe to administer the drug in the usual doses. As prophylaxis against ventricular tachycardia, 3-grain doses of quinidine sulfate four times daily have been employed. Larger doses may be required, and in some cases it has been necessary to administer as much as 60 grains daily. The first case was adequately controlled without recurrences of ventricular tachycardia on 30-grain doses of quinidine sulfate daily. No toxic symptoms resulted from the administration of the 54-grain doses of quinidine sulfate daily in the second case although it failed to prevent the recurrence of the ventricular tachycardia.

The earliest electrocardiographic change in a patient receiving oral quinidine sulfate is a prolongation of the QRS interval. In one of Gold's¹⁶ patients, receiving a dose of 50 to 60 grains of quinidine sulfate daily, the QRS interval which was originally 0.12 second later became prolonged to 0.16 second and it never went above this; in none of our tracings did the QRS interval become longer than 0.10 second. There is seldom a prolongation of the QRS interval over 0.12 second unless the patient is receiving more than 30 grains of quinidine daily. The cumulation of quinidine ceases in a very few days with a fixed dose and usually after the fifth day the quinidine level reaches its maximum.

The oral administration of quinidine may not control the ventricular tachycardia, and quinidine may have to be administered intravenously as a lifesaving procedure. The patient usually reacts quite violently to the intravenous administration. In our cases it was not uncommon for the patient to feel excessively warm, to have a profuse diaphoresis with a cold, clammy skin, and often rather severe nausea and vomiting. In Case 1 a generalized convulsion occurred concomitantly with the absence of audible heart sounds. Schwartz and Jezer¹⁷ noted that, with the intravenous administration of either quinine dihydrochloride or quinidine sulfate, either a prefibrillation mechanism or transient periods of ventricular fibrillation frequently developed. In their experience, once the prefibrillation mechanism was precipitated by the adminis-

tration of drugs, recurrent periods of transient ventricular fibrillation sometimes followed for several hours. They found also that there was a more rapid appearance of ventricular fibrillation when ventricular premature beats were already present. They, therefore, thought that the usage of quinine and its derivatives was definitely contraindicated for intravenous administration. I have used a preparation of quinidine lactate intravenously in doses varying from 5 to 20 grains. Although moderately severe subjective symptoms were obtained, the ultimate goal of relieving the ventricular tachycardia was reached in many instances, and in none of them did death occur. Perhaps failure to get response to the quinidine either orally or intravenously in the second case was due to the possibility that the origin of the tachycardia was a circus movement about the base of the aorta, perhaps giving a ventricular type of electrocardiographic tracing. On the one occasion in which lanatoside C was administered intravenously, a rather prompt restoration of the normal mechanism occurred. No explanation for this is given, but I have observed this phenomenon following the intravenous administration of lanatoside C in paroxysmal auricular tachycardia in a young child uncontrolled by the methods for treating supra-ventricular tachycardia.

SUMMARY

Two cases of ventricular tachycardia treated by the intravenous administration of quinidine lactate are reported. The possible etiological factors, diagnostic difficulties, and electrocardiographic findings in ventricular tachycardia are presented. The oral and intravenous administration of quinidine are discussed, also.

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PREMATURE BEATS OF SINUS ORIGIN

ELECTROCARDIOGRAPHIC DEMONSTRATION OF A CLINICAL CASE

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PREMATURE cardiac systoles have been induced artificially and may theoretically arise physiologically from any portion of the auricles or ventricles, including the A-V node and bundle and, presumably, from the sino-auricular node, also. All varieties of premature beats, *except the last*, are usually readily recognized and demonstrated by ordinary electrocardiographic means. No illustrations of premature beats of sinus origin appear in any of the modern treatises on electrocardiography, and no proved clinical instance seems, thus far, to have been presented in the general medical literature.*

Sinus premature beats may be defined electrocardiographically as premature systoles whose auricular and ventricular deflections in all leads are indistinguishable from those characteristic of the basic sinus rhythm; moreover, the returning cycle following a sinus premature systole should be no longer than the initial cycle. Obviously, premature beats of sinus origin must be differentiated from sinus arrhythmia, from periodic sinoauricular block or auricular standstill, and from certain auricular premature beats; and the acceptability of any case presented as one of sinus premature beats will depend upon how convincingly one may be able to exclude these commoner and more familiar arrhythmias in a case which also meets the established criteria.

The following clinical description concerns a patient who manifested an arrhythmia which we concluded, after particular study, to be due to sinus premature beats.

S. S., a 64-year-old man, had first entered the New Haven Hospital in September, 1942, with empyema in the left side of the chest; this was drained by a thoracotomy, and convalescence was uneventful. In April, 1944, he had a large hematemesis. A history of dysphagia and progressive weakness dating back about sixteen months was obtained. More recently there had been moderate shortness of breath and slight swelling of the ankles. Examination revealed moderate cardiac enlargement, soft aortic and apical systolic murmurs, coupled rhythm with the radial pulse wave of the second beat in each couplet palpably weaker than the first, slight dependent edema, and râles in small numbers at each lung base. The blood pressure was normal (125/65) and there was no ascites or enlargement of the liver. A significant anemia (red blood cells, 3.7 million per cubic millimeter, hemoglobin, 9 Gm.) and hypoproteinemia (5.6 Gm. per cent) were found. Esophagoscopic examination and biopsy disclosed cancer of the esophagus. After transfusion and six days of rest in bed the edema and dyspnea subsided, the murmurs disappeared, but the coupled rhythm persisted without apparent intermission throughout the patient's stay. Treatment was declined, and the patient was discharged after twelve days in the hospital.

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*Sir Thomas Lewis' illustration of a sinus premature systole on page 229 (Fig. 205) of his classical monograph, *The Mechanism and Graphic Registration of the Heart Beat* (London, 1925, Shaw and Sons, ed. 3), shows a single premature beat in but one lead, the premature P wave is, unfortunately, superimposed on the T wave of the preceding cycle, and the successive P waves in the tracing exhibit considerable variation in amplitude. It is difficult, under the circumstances, to accept the essential argument that the premature P wave in question is identical with the P waves of the regular cycles.

The electrocardiogram taken initially to analyze and identify the coupled rhythm is shown in Fig. 1; the diagnosis of coupling due to sinus premature beats was ventured after completion of the special studies that follow.

Our opinion that the coupled rhythm manifested in the case described was due to regularly recurring premature beats of sinus origin was based upon (1) their conforming to the criteria for sinus premature beats, and (2) our ability to exclude the following arrhythmias which intrude on the differential diagnosis.

Simple Arrhythmia of Sinus Origin.—This may be defined as an irregular succession of otherwise normal cardiac cycles. Electrocardiographically, normal auricular deflections are followed after normal A-V conduction times by ventricular complexes, but the successive cycles are unevenly spaced. Two varieties are generally recognized: (1) phasic sinus arrhythmia, which reveals itself in cyclic variations in rate whose periods are obviously related to respiration; holding the breath is generally believed to eliminate this arrhythmia; and (2) nonphasic sinus arrhythmia, in which a respiratory association may not ordinarily be evident but is usually made obvious through the exaggerated influence of deep breathing.

Our case was remarkable in exhibiting coupled rhythm composed of apparently identical auricular and ventricular complexes with only an infrequent and unpredictable momentary interruption of the coupling by the occurrence of three cycles that were very nearly evenly spaced (indicated by brackets in Fig. 1, Lead II). Such persistent bigeminy is not a familiar expression of sinus arrhythmia.

Phasic sinus arrhythmia seemed further excluded because no cyclic variation with respiratory correlation was evident even in strips recorded continuously for more than thirty seconds during normal respiration at a rate of 15 per minute. Moreover, the length of the phases represented by the coupling of the beats was too brief (1.62 seconds) to be correlated with the duration of the respiratory cycles (which averaged about 4 seconds). Finally, the arrhythmia was not abolished by holding the breath (Fig. 1, Lead III).

Nonphasic sinus arrhythmia seemed excluded not only by the practically unvarying constancy of the time relations within and between the successive cycles of coupled beats, but also by the fact that deep breathing abolished rather than exaggerated the arrhythmia during the first seven seconds of the expiratory phase (Fig. 2). Finally, acceleration of the heart rate by mild exertion failed to stop the arrhythmia, as is seen in Fig. 3b, which was recorded after several sit-ups in bed. Moreover, the coupling apparently persisted throughout twelve days of hospitalization during which the patient was allowed full activity on the ward, and during which he exhibited pulse rates varying from 60 to 90. On the basis of this evidence we consider sinus arrhythmia excluded from the differential diagnosis.

Periodic Sinoauricular Block (Auricular Standstill).—Failure of the sinus node to activate the auricles, with resultant nonappearance of a P wave, is usually regarded as due either to increased vagal tone inhibiting the sinoauricular node or depression of the normal pacemaker by drugs, infections, or direct injury. Theoretically, sinoauricular block recurring regularly following two normal cycles could produce coupled rhythm like that illustrated. Another hypothetical situation involving sinoauricular block could be postulated if one assumed that the sinus node might be discharging at twice the rate (every 0.33 second) represented by the short cycles (0.66 second) and that one sinus discharge within the short cycle is blocked. The long cycles would then pre-

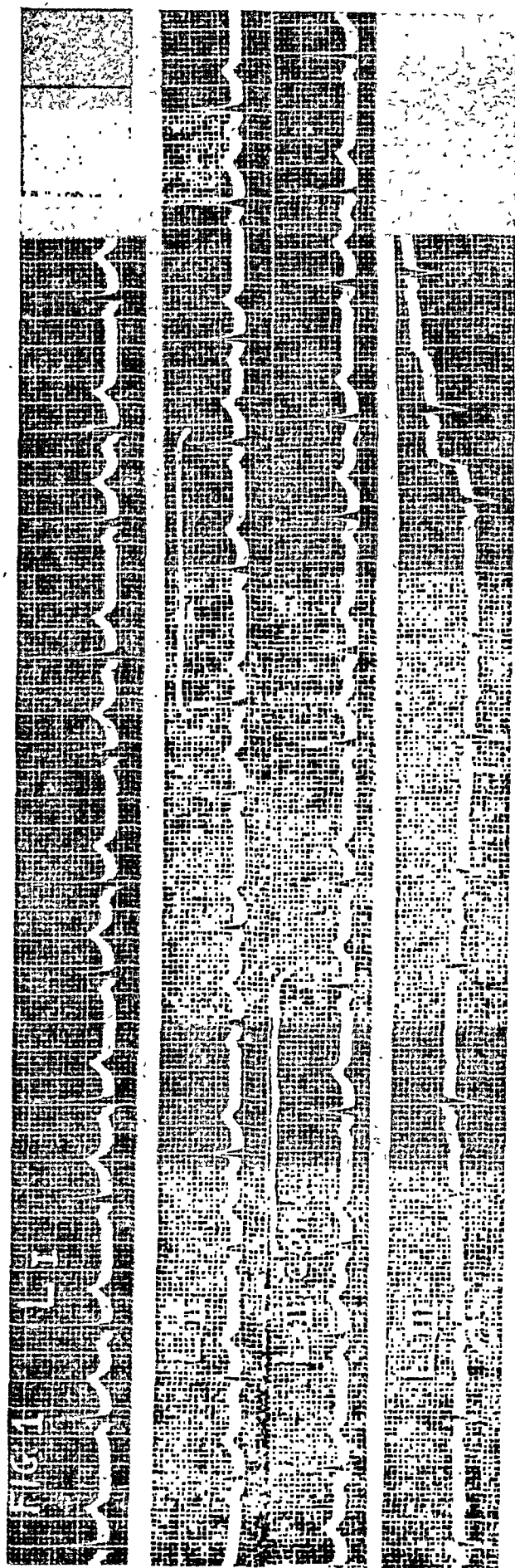


Fig. 1.—Standard limb lead electrocardiogram showing uninterrupted coupled rhythm in Leads I and II, while in Lead II the coupling is interrupted twice (within brackets) by two cycles of apparently normal sinus rhythm. Breath was held during the recording of Lead III.

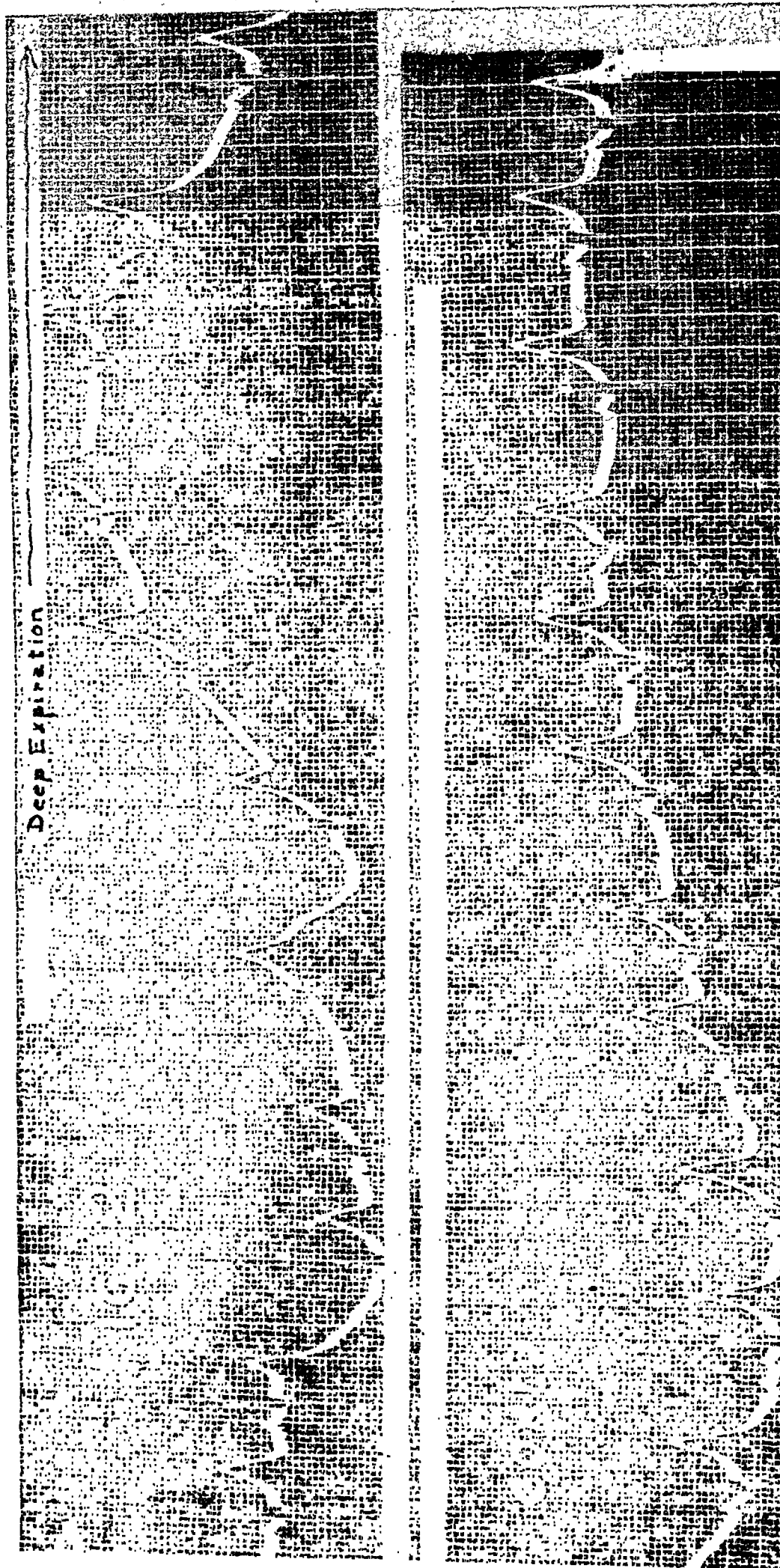


Fig. 2.—Semidirect electrocardiogram obtained from chest wall with right and left arm electrodes over third and fifth intercostal spaces, respectively, adjacent to sternal margin. During sustained expiration, indicated by white stripe, the coupled rhythm was abolished for seven seconds.

sumably result from the blocking of two successive sinus discharges. The long cycles should, under these circumstances, be 0.99 second apart. Actual measurement of the P-R intervals of the long cycles in Fig. 3a and 4, which offers the advantage of amplified auricular deflections for precise measurement, does in fact yield almost exactly, but perhaps fortuitously, this predicted value (actually 0.96 second). However, to accept the hypothesis as proved by this argument it becomes necessary to accept a fundamental sinus discharge rate of 182 per minute as implied by the assumed cycle length of 0.33 second. It appeared hazardous to invoke two extraordinary disturbances in rhythm to explain the bigeminy in this case, particularly since the diagnosis of sinoauricular block, whether with or without the hypothetical tachycardia, seemed untenable from the following observations:

1. S-A block presents itself usually as isolated dropped beats occurring irregularly, or as more sustained periods of auricular standstill, and not as a regularly intermittent phenomenon with the production of coupled rhythm.

2. The usual toxic influences (digitalis, quinidine, infections) which produce S-A block were not present.

3. Failure of the arrhythmia to be diminished or abolished by a "sympathicotonic" influence like exercise (Fig. 3b) is atypical behavior for S-A block.

4. The temporary abolition of the arrhythmia by a "vagotonic" influence like deep expiration following a full inspiration (Fig. 2) is contrary to the behavior of S-A block which should be intensified by such a maneuver.

Sinoauricular block appeared excluded from the differential diagnosis by the considerations mentioned.

Auricular Premature Systoles.—The fundamental electrocardiographic characteristics of this irregularity are a premature P wave that usually differs at least slightly in form from the subject's normal or natural auricular deflection, and a P-R interval at least 0.12 second long, and usually as long or longer than the average A-V conduction for the subject. The nearer the ectopic auricular focus lies in relation to the sinus node, the closer may be the resemblance of the auricular phenomena recorded electrocardiographically from the normal and the abnormal focus.

Careful inspection of the P waves and P-R intervals throughout each of the three standard limb leads (Fig. 1) reveals no detectable differences, however minor, in the course of any one lead. This implies that the auricular waves in each couplet have a common site of origin, and since the P waves throughout are of normal configuration, amplitude, and direction, the designation of a sinus origin for the premature beats seems warranted.

It must be acknowledged that, under circumstances of extreme adjacency of an ectopic auricular focus and the sinus node, the P waves resulting from auricular excitation in each instance (and their P-R intervals) may be remarkably similar. However, minor changes in the appearance of the P waves may theoretically be expected, even when the site of the impulse formation is shifted within the sinus node; and it is conceivable that very slight differences may not be recorded by the peripheral limb leads of conventional electrocardiographic technique, which admittedly reproduces the auricular deflection relatively inadequately as a small monophasic deflection instead of as a complex of two or more phases that are revealed by direct leads.

In order, therefore, to investigate the details of the P waves and P-R intervals more precisely in our case and to verify their identity or reveal slight differences, we obtained semidirect leads from the chest wall and then further ampli-

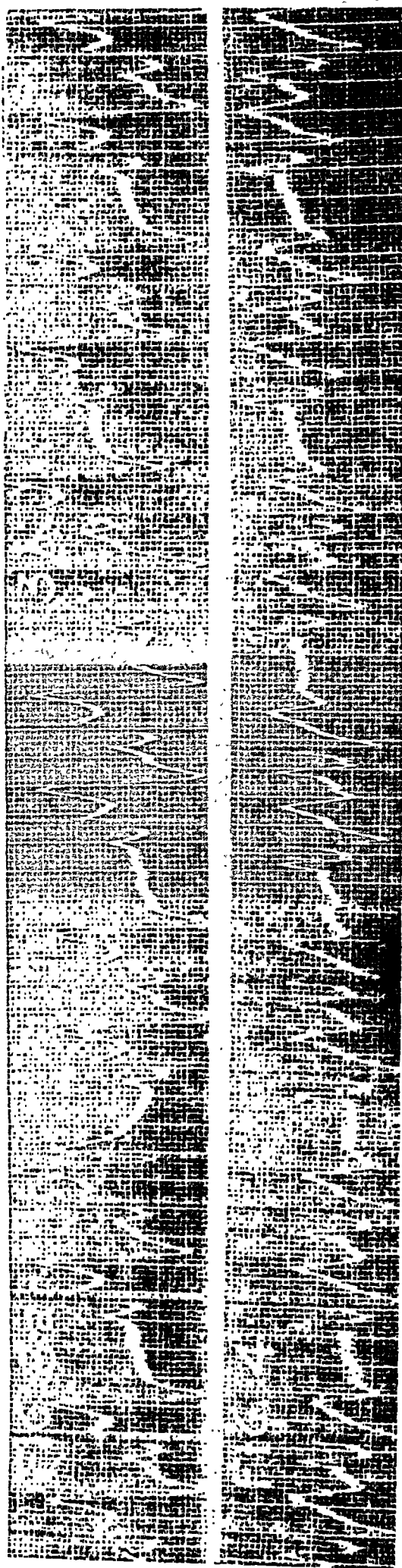


Fig. 3a.—Amplified electrocardiogram obtained by placing right and left arm electrodes over third and fifth intercostal spaces, respectively, adjacent to right sternal margin, and amplified about fourteen times; 3b, same, after mild exercise.

Fig. 4.—Amplified electrocardiogram obtained by placing right and left arm electrodes over third right and left intercostal spaces, respectively, adjacent to sternal margin.

fied the resulting electrocardiogram. This was done by placing the arm lead electrodes in contact with the chest wall in the third and fifth intercostal spaces at the right margin of the sternum, and also in the third intercostal spaces at the right and left margins of the sternum. The right arm terminal and electrode in either placement occupied the upper or the right-sided position. Further amplification of the resulting augmented deflections was obtained by interposing a single-stage resistance-coupled amplifier, described previously,¹ in the lead line between the patient and the electrocardiograph.* The auricular deflections so obtained were about fourteen times larger than those recorded by the limb leads and, as expected, they exhibited a more complex and diphasic character permitting more detailed study (Figs. 3 and 4).

Inspection of these amplified P waves again revealed a remarkable identity in form within each couplet. Such minor differences as could occasionally be discovered were found to prevail also between the P wave contours of successive beats whether in the premature or normal position; they were probably slight artefacts resulting from the high amplification. Moreover, the P-R intervals, which permitted exceptionally precise measurement in the amplified records, also proved to be remarkably similar in differing only occasionally and by not more than 0.02 second throughout the records. Finally, to exclude the possibility that the premature cycle might arise from an extrasinus focus which happened to be exactly the same distance from the A-V node as the S-A node for the chosen (vertical) plane of the lead-off points, amplified electrocardiograms were repeated for the opposite (horizontal) plane; these records also verified the constancy of the A-V conduction time for the normal and premature cycles and again revealed the identity of P-wave contour for the two auricular deflections in each couplet.

These observations, fortified by the evidence obtained from the amplified electrocardiograms, seem to establish that the premature beats arose within the sinus node, and that their precise point of origin was identical with the site of the normal pacemaker in this case.

COMMENT

The cause of the sinus premature beats in our case was not evident. The patient was not critically ill, his nutritional state was good, and the only objective finding of possible cardiovascular interest was transient edema of the ankles and a moderate anemia. The alleviation of the anemia with two transfusions, which restored the hemoglobin level to 12 Gm. (78 per cent), did not apparently affect the arrhythmia. The only medications included moderate doses of aspirin for five days, and an almost nightly soporific of pentobarbital (0.1 Gm.), a single dose of morphine (0.01 Gm.) in preparation for esophagoscopy examination, and moderate daily doses of thiamine and of vitamin B complex (brewers' yeast). None of these medications could conceivably have induced the constant arrhythmia. From bronchoscopic and roentgenographic examinations there was no evidence that the esophageal cancer had infiltrated the mediastinum, there was no clinical indication of pericardial effusion, and there was no deformity of the contour of the heart in the roentgenograms to suggest invasion by cancer.

SUMMARY

An elderly man with cancer of the esophagus presented coupled rhythm apparently continuously during twelve days of observation, and electrocardio-

*"Cardiette," Sanborn Company.

graphic study employing auricular amplification techniques led to the diagnosis of regularly recurring premature beats of sinus origin. To our knowledge, this is the first convincing demonstration of sinus premature beats occurring clinically. The cause for the arrhythmia was not apparent.

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INCOMPLETE HEART BLOCK PRODUCED BY CHANGES IN POSTURE

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ARMY OF THE UNITED STATES

THE relation of second degree heart block to posture was brought to our attention by the first of our cases listed below. Shortly afterward a case of first degree heart block was noted in routine examination, and when studied the P-R interval was found to vary with posture. In both of these cases heart block was abolished when the subject assumed the upright position. A third case, one of first degree heart block in which the block was not influenced to a major degree by posture, is included for comparison.

Review of the literature has revealed one case reported by Alexander and Bauerlein¹ in which heart block was observed in the supine position and disappeared in the standing position. Poel² reported a case of first degree heart block which showed variations of P-R interval with posture. Poel² also cites three cases of vagal effect on incomplete heart block from the literature, but the effects of posture were not given.

REPORT OF CASES

CASE 1.—The patient was a white man, aged 22 years. During routine altitude indoctrination on May 5, 1944, in a low-pressure chamber this man suffered "bends" at a simulated altitude of 30,000 feet. During descent to ground level the subject was in a sitting position, and the character of the pulse was weak, rhythmic, and regular. Upon reaching ground level he was transferred to a bed and placed in the supine position. When examined in this position the pulse exhibited weakness, arrhythmia, and irregularity in that there was a dropping of every third to fourth beat. The pulse rate at that time was 78 per minute. The blood pressure was 130/76. After an hour of rest in bed and the administration of oxygen at the rate of 6 liters per minute the subject was allowed to stand. Since the pulse was rhythmic and regular, and the blood pressure was 122/70 while he was in the standing position, the soldier was considered free from any ill effects of aero-embolism and was therefore returned to duty. Three days later a recheck of simulated altitude flight was made. Again the soldier suffered from "bends" at 30,000 feet and was brought quickly to ground level. Examination on descent in the escape-lock showed the pulse to be rhythmic and regular (rate, 72 per minute), but on placing the subject in the supine position irregularity of the pulse with dropped beats was noted. An electrocardiogram was made in the supine position at that time (Fig. 1). After an hour of rest in bed and oxygen therapy the patient was permitted to stand, and the pulse was noted to have lost its irregularity and arrhythmia. In the absence of any other cardiac symptom or sign it was suspected that the above irregularity was on a postural basis. This was confirmed when it was found that the irregularity could be reproduced at will by placing the subject in the supine position and that on standing or sitting the pulse again became regular. The soldier was discharged to duty but ordered to return daily so that he could be observed. During each visit the electrocardiographic tracings were repeated in the supine, sitting, and standing positions (Fig. 2).

Past Medical History.—The patient had had the usual childhood diseases. There was no history of rheumatic fever, scarlet fever, or diphtheria. Tonsillectomy and adenoidectomy were performed at the age of 6 years. Fracture of the nose had occurred at the age of 8 years, with plastic operation on same at the age of 20. At the age of 15 years he was struck in the left eye with a potato fork; this resulted in loss of vision in the eye without loss of the globe. At the age of 17 years he sustained "steering-wheel" compression of the chest, but no fracture of the ribs or sternum. Family and marital histories were negative. System history was negative.

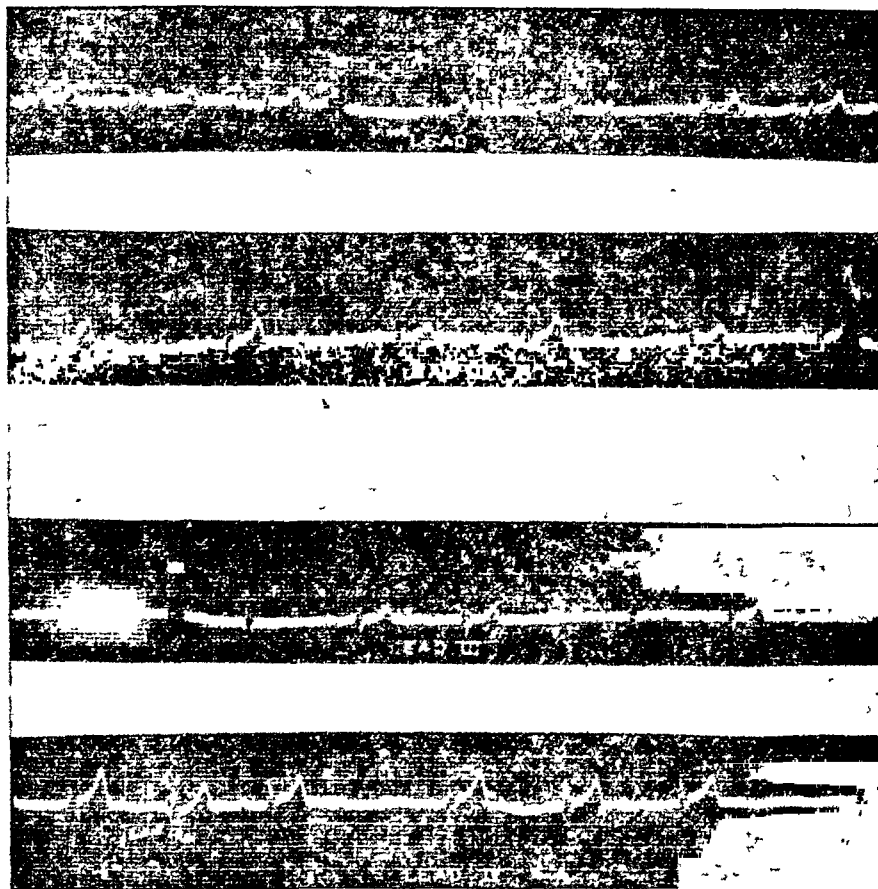


Fig. 1.—Electrocardiographic tracing of Case 1 made in supine position thirty minutes after descent from simulated altitude of 30,000 feet in low pressure chamber (May 8, 1944) showing Wenckebach phenomenon. (Photo by U. S. Army Air Forces, Flying Training Command, Buckingham Army Air Field, Fort Myers, Florida.)

Physical Examination.—Height, 72½ inches; weight, 173 pounds; head, negative; ears, negative; eyes, O. D. 20/20, O. S. 20/800, pupils equal, O. D. reacted to light and in accommodation, O. S. sluggish to light, extraocular movements normal; nose, negative; mouth, teeth in fair condition; chest, lungs clear; heart, not enlarged, sounds of good quality, no murmurs; abdomen, negative; extremities, negative; neurological examination, negative. Laboratory examination: Kahn, negative; urinalysis, negative; x-ray of chest including fluoroscopy of the heart in the supine and upright positions and examination of the esophagus and cardiac shadow with the aid of contrast media revealed no gross abnormality. No true intrinsic lesion or intraluminal lesion of the esophagus could be observed. The cardiac silhouette appeared rather globular, but was considered to be within normal limits. No evidence of chamber enlargement could be discerned.

Electrocardiographic Examinations.—The first tracings, taken in the supine position (Fig. 1), show an auricular rate of 75 and a ventricular rate of 54. The P-R interval increases progressively from 0.16 to 0.36 second, and is followed by a P wave without a ventricular complex. The next ventricular complex is of abnormal contour. In some phases it is preceded by a P-R interval of less than 0.12 second, or the P wave may be superimposed on the QRS complex (lower nodal rhythm). Three days later tracings were made in various positions with the results as follows (Fig. 2): Standing position (Fig. 2, A), normal electrocardiogram with auricular and ventricular rates of 79 and P-R interval of 0.20 second.

Immediately upon assuming the supine position (Fig. 2, *B*) there is a transition from the normal electrocardiogram to one exhibiting Wenckebach phenomenon. The electrocardiogram taken after a period of time in the supine position (Fig. 2, *C*), shows Wenckebach phenomenon with ventricular escape. The P-R interval progresses from 0.16 to 0.36 second. Some of the complexes of ventricular escape show superimposed P waves similar to those seen in Fig. 1.

Tracings made in the sitting position were similar to those made in the standing position. In both the supine and standing positions, carotid sinus pressure and eyeball pressure had no effect. Tracings made on the stomach, back, and either side were identical. Sleep did not abolish the Wenckebach phenomenon. All the above studies were repeated fourteen and eighty-three days later, and the results were identical. Further electrocardiographic studies were made under $\frac{1}{50}$ grain of atropine, given subcutaneously, on Aug. 31, 1944. The drug completely abolished the increased P-R interval and the Wenckebach phenomenon. The P-R interval was 0.16 second, and the heart rate 100 per minute. The effect of exercise was studied and was found to be dependent upon the degree of exertion. Immediately following exercise the subject was placed in the supine position and tracings were made. The increased P-R interval and Wenckebach phenomenon were unaffected by mild exercise, but abolished by vigorous exercise.

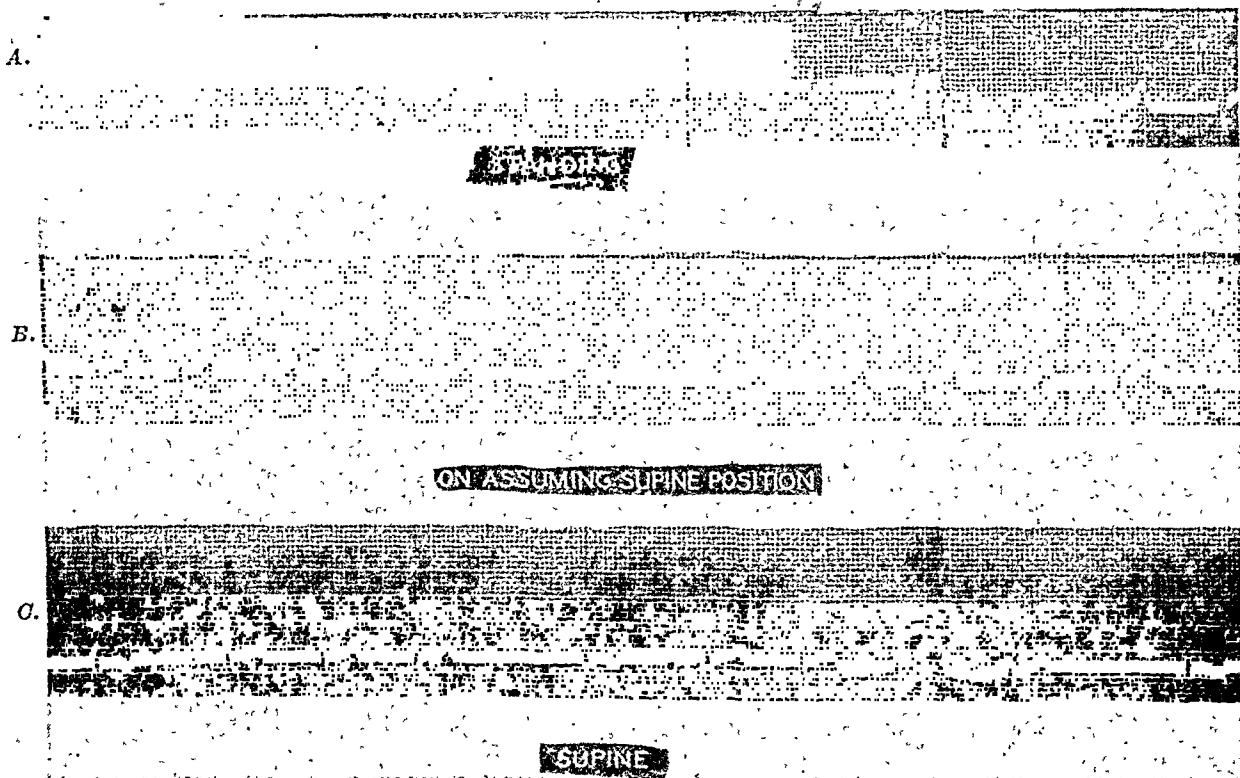


Fig. 2.—Electrocardiographic record of Case 1 showing tracing made *A*, in standing position, *B*, on assuming supine position, and *C*, after a period of time in supine position. *B* and *C* show Wenckebach phenomenon, and *C* also shows ventricular escape. (Photo by U. S. Army Air Forces, Flying Training Command, Buckingham Army Air Field, Fort Myers, Florida.)

CASE 2.—The patient was a white man, aged 22 years. During routine electrocardiographic study for duty as inside observer in an altitude chamber, it was noted that this man exhibited a P-R interval of 0.40 second. Questioning revealed no symptoms referable to the cardiovascular system, and in supervised exercise he was equal to other members of his unit. Because of the interest aroused by the previous case (Case 1) similar studies were carried out on this man.

Past Medical History.—The past medical history was essentially negative except for childhood diseases, appendectomy, tonsillectomy, and adenoidectomy. Marital and family histories were not contributory.

Physical Examination.—Height, 68½ inches; weight, 150 pounds; head, negative; eyes, 20/20 vision bilaterally, pupils equal, react to light and in accommodation, extra-ocular movements normal; ears, normal, hearing 20/20 bilaterally; nose, normal; teeth, fair; nasopharynx, normal; tonsils, enucleated; lungs, clear; heart, not enlarged, sounds of good quality, no murmurs, pulse 72 per minute, blood pressure 118/76; abdomen, negative; genitourinary system, negative; extremities, negative; neurological examination, negative. Labora-

tory examination: Kahn, negative; urinalysis, negative; blood counts within normal limits. Special radiological examination showed the cardiac silhouette within normal limits and no abnormalities of the mediastinum and esophagus.

Electrocardiographic Examination.—The first tracings taken in the supine position (Fig. 3, A), show an auricular rate of 79 and a ventricular rate of 79. The P-R interval is 0.40 second. Records taken in the *supine position immediately after exercise* (Fig. 3, C) (two-step exercise of Masters and Oppenheimer³), showed a heart rate of 75 and P-R interval of 0.19 second. With the subject in the supine position, pressure was applied to the right carotid sinus. The tracing (Fig. 3, D) showed the heart rate to slow from 75 to 62 and the P-R interval to decrease from 0.37 to 0.17 second. Similar changes were exhibited by eyeball pressure. Observations made in the supine position after atropine ($\frac{1}{50}$ grain subcutaneously) showed a decrease of the P-R interval to 0.20 to 0.21 second in all records where there was an increased cardiac rate.

Tracings made in the sitting position were similar to those made in the standing position, and showed a normal P-R interval of 0.16 second (Fig. 3, B). Tracings made while on the stomach, on either side, or supine were identical. All studies were repeated over a period of twenty days.

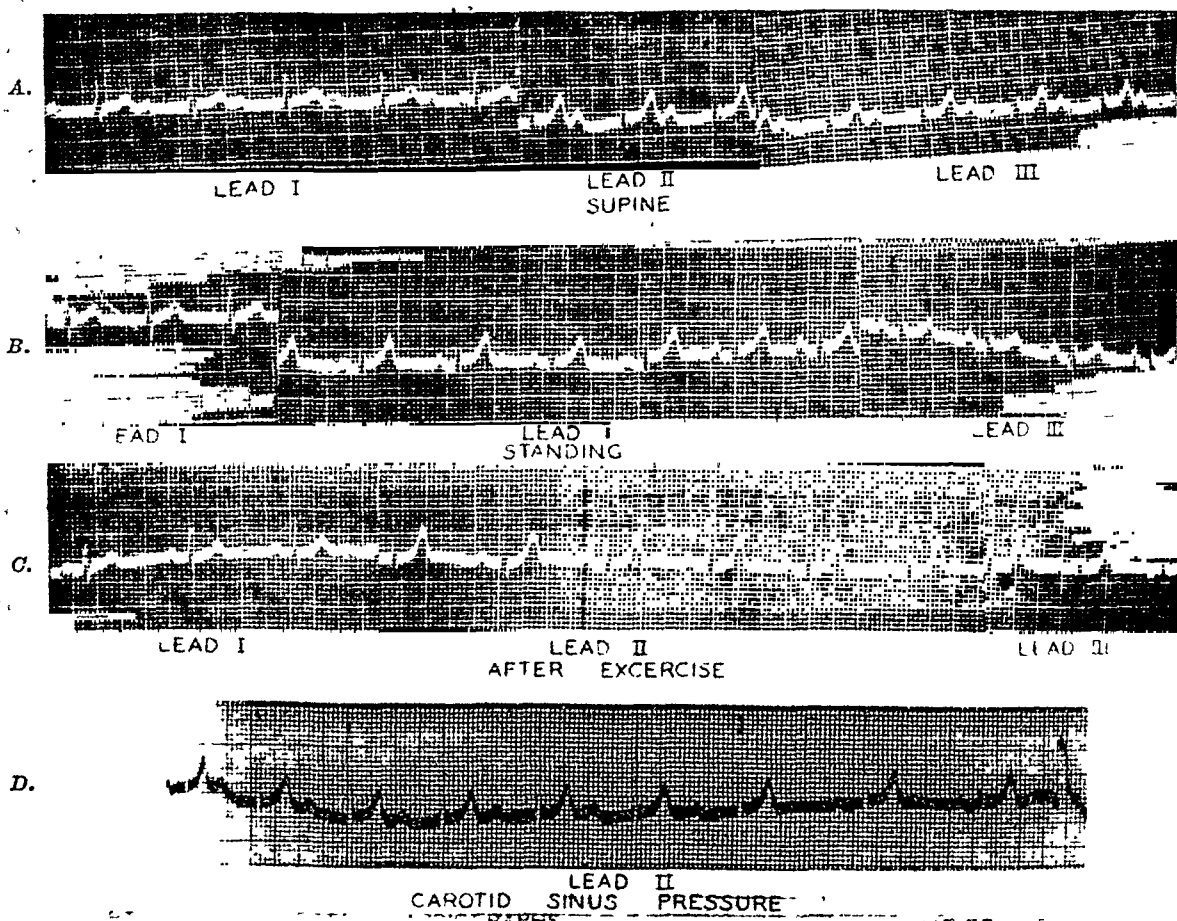


Fig. 3.—Electrocardiographic tracings of Case 2, showing A, prolonged P-R interval in supine position, B, normal P-R interval in standing position, C, normal P-R interval in supine position immediately after exercise, and D, decrease of P-R interval following right carotid sinus pressure as noted in last two cardiac cycles. (Photo by U. S. Army Air Forces, Flying Training Command, Buckingham Army Air Field, Fort Myers, Florida.)

CASE 3.—The patient was a white man, aged 27 years. During routine electrocardiographic study for duty as inside observer in an altitude chamber on Sept. 4, 1943, it was noted that this man exhibited a P-R interval of 0.40 second. Questioning revealed no symptoms referable to the cardiovascular system, and, like the preceding cases, his exercise tolerance showed him equal to other members of his unit. Because of the interest aroused by the preceding cases this man was re-examined and studied in a similar manner.

Past Medical History.—He had had the usual childhood diseases including diphtheria and scarlet fever. There was no history of rheumatic fever. Tonsillectomy and adenoidectomy.

tomy had been performed when he was 5 years old. He had suffered a fractured nose in 1936. Family and marital histories were not contributory.

Physical Examination.—Height, 70 inches; weight, 152 pounds; head, negative; eyes, vision 20/20 bilaterally, pupils equal and react to light and in accommodation; ears, negative, hearing 20/20 bilaterally; nose, normal; teeth, fair; lungs, clear; heart, not enlarged, sounds of good quality, no murmurs, pulse 64 per minute, blood pressure 108/58; abdomen, negative; genitourinary system, negative; extremities, negative; neurological examination, negative. Laboratory examination: Kahn, negative; urinalysis, negative; blood counts within normal limits. Radiological examination showed the heart normal in size and shape and the mediastinum and esophagus within normal limits.

Electrocardiographic Examination.—Tracings (Fig. 4, A) taken in the supine position on Aug. 24, 1944, show a heart rate of 62 and a P-R interval of 0.36 second. The P waves and QRS complexes are normal. There is a slight elevation of the S-S-T₂ segment. Tracings made in the standing position show a rate of 81 per minute and the P-R interval is 0.28 second (Fig. 4, B). The S-S-T₂ segment is slightly elevated and the T₂ is diphasic. A tracing made after performance of the two-step exercise of Masters and Oppenheimer³ shows a P-R interval of 0.28 second. A tracing made after right carotid sinus pressure shows a heart rate of 36 per minute (control rate, 62 per minute), and the P-R interval changed from 0.36 second to 0.28 second (Fig. 4, C). In no tracing in this study were there any dropped beats. A tracing made in the supine position after the administration of atropine ($\frac{1}{50}$ grain subcutaneously) showed reduction of the P-R interval from 0.36 to 0.28 second and a heart rate of 79 (control rate, 68).

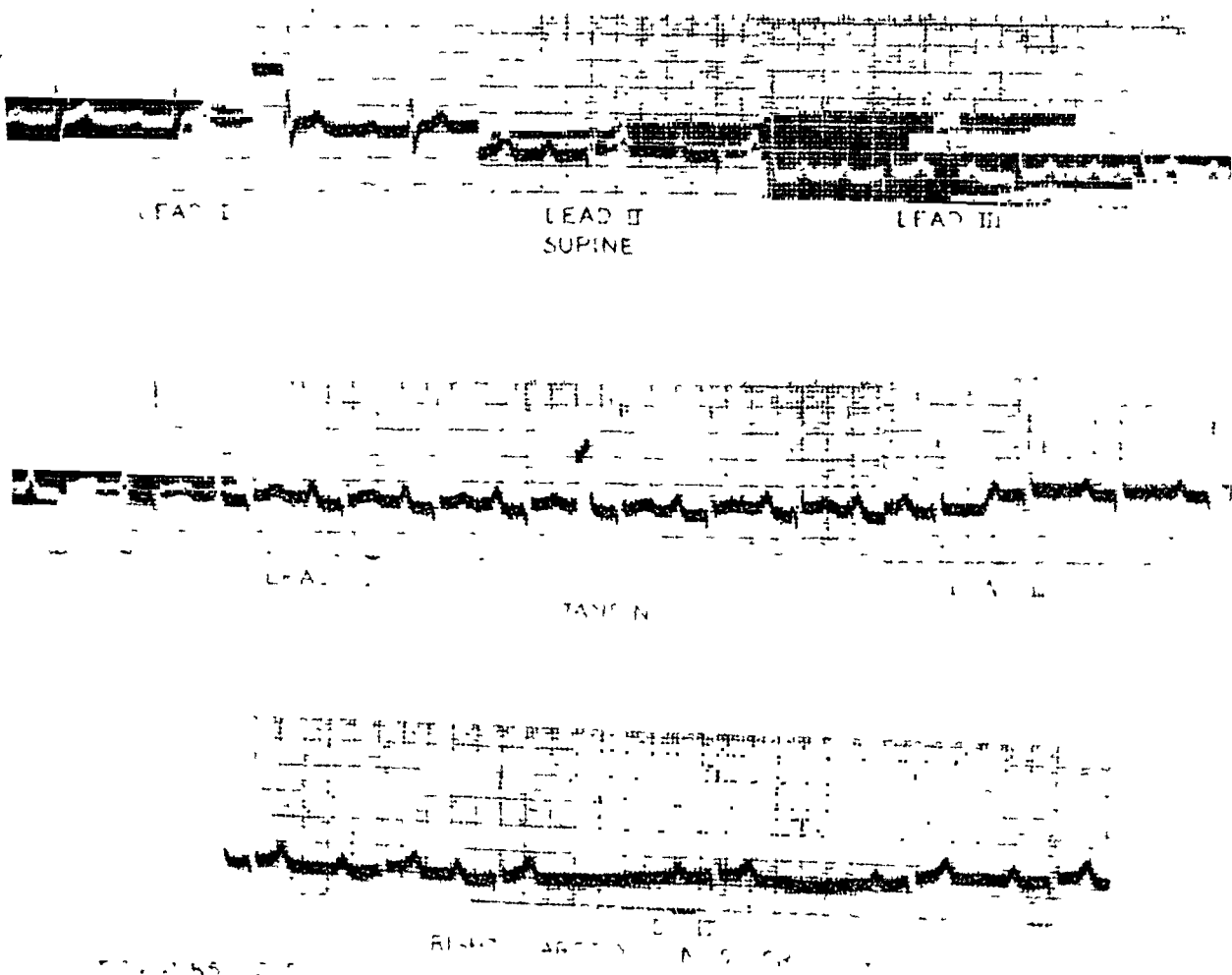


Fig. 4.—Electrocardiographic tracings of Case 3, showing A, prolonged P-R interval in supine position, B, prolonged P-R interval in standing position, and C, effect of right carotid sinus pressure. (Photo by U. S. Army Air Forces, Flying Training Command, Buckingham Army Air Field, Fort Myers, Florida.)

DISCUSSION

The important features of these cases are listed in Table I. In all three cases there was marked prolongation of the P-R interval in the supine position. (In Case 1, the P-R interval increased progressively from 0.16 to 0.36 second,

TABLE I. A COMPARATIVE STUDY OF CHANGES IN P-R INTERVAL IN THE THREE CASES REPORTED

	CASE 1	CASE 2	CASE 3
AGE (YRS.)	22	22	27
SUPINE	Heart rate: auricular, 75; ventricular, 54. Progressively increasing P-R interval, 0.16 to 0.36 second	Heart rate, 79. P-R interval, 0.36 to 0.40 second	Heart rate, 62. P-R interval 0.36 second
STANDING	Heart rate: auricular, 79; ventricular, 79. P-R interval, 0.20 second	Heart rate, 79. P-R interval 0.16 second	Heart rate, 81. P-R interval 0.28 second
WENCKEBACH PHENOMENON WHEN SUPINE	Present	Not present	Not present
ATROPINE (SUPINE POSITION)	Heart rate: auricular, 100; ventricular, 100. P-R interval, 0.16 second	Heart rate, 100. P-R interval, 0.20 to 0.21 second	Heart rate, 79. P-R interval 0.28 second
CAROTID (RIGHT) SINUS PRESSURE (SUPINE POSITION)	No change	Heart rate, 62. P-R interval 0.17 second	Heart rate, 36. P-R interval 0.28 second
EYEBALL PRESSURE (SUPINE POSITION)	No change	Heart rate, 62. P-R interval 0.17 second	No change
TWO-STEP EXERCISE (SUPINE POSITION)	Heart rate, 71. P-R interval, 0.16 second	Heart rate, 75. P-R interval 0.19 second	Heart rate, 80. P-R interval 0.28 second

with Wenckebach phenomenon; in Case 2, the P-R interval was 0.36 to 0.40 second; and in Case 3, the P-R interval was 0.36 second.) On standing the P-R interval of the first two cases returned to normal limits while the third dropped to 0.28 second.

The characteristic sequence of lengthening of A-V conduction time with eventual dropping of a ventricular beat was first described by Wenckebach.⁴ This phenomenon was noted in only one of our cases. (In Case 1 the P-R interval increased progressively from 0.16 to 0.36 second, with dropping of ventricular beat.)

In order to evaluate the vagal influence in these cases, atropinization ($\frac{1}{160}$ grain subcutaneously) was done. In the first two cases the prolonged P-R intervals were restored to normal limits (Case 1, P-R interval 0.16 second; Case 2, P-R interval 0.20 to 0.21 second). In the third case the P-R interval did not return to normal limits (Case 3, P-R interval 0.28 second). However, one must view with caution the concept that positional change followed by a decrease in P-R interval is completely one of variations in vagal influence. The records show that the reduction of P-R interval with change in posture can occur without change in rate.

Studies were made on the effect of right carotid sinus and eyeball pressure. In Case 2 the P-R interval changed from 0.37 to 0.17 second; in Case 3 the P-R interval dropped from 0.34 to 0.28 second. There was no change in Case 1.

The subjects were exercised according to the two-step exercise of Masters and Oppenheimer;⁵ immediately afterward they were placed in the supine position, and electrocardiographic tracings were made. In Cases 1 and 2 the P-R interval was within normal limits (Case 1, P-R interval 0.16 second; Case

2, P-R interval 0.19 second). Exercise of a lesser degree than the "two-step exercise" in Case 1 showed no effect on the Wenckebach phenomenon. In Case 3 the P-R interval decreased from 0.36 to 0.28 second.

Our three cases have been those of healthy adult males, able to carry on full military activity, and free of any cardiac symptoms. Their discovery was on routine basis. In Case 3 the finding of first-degree heart block was apparent in any position. However, in the other two cases, physical and electrocardiographic studies done in the sitting or standing positions would have been negative, whereas in the supine position both showed positive electrocardiographic findings, and one showed a physical sign. Our experience with these two subjects suggests that, for proper evaluation, all cases of first and second degree heart block should be examined in both the upright and supine positions.

In consideration of the data in Case 3 it is our opinion that, in this instance, the physiologic lower limit of A-V conduction time is 0.28 second. This conclusion is based on our finding that atropinization, carotid sinus and eyeball pressure, exercise, and standing will not reduce the P-R interval below 0.28 second. In Cases 1 and 2, A-V conduction time can be lowered to within normal limits by standing, by atropinization, by exercise and, in Case 2, by carotid sinus and eyeball pressure. Evidence from these two cases suggests that the P-R interval can have a wide physiologic range.

Data from three somewhat similar cases reported in the literature are summarized in Table II. It will be noted that Alexander and Bauerlein¹ thought their case to be one of early heart block of organic etiology whereas the other two cases were in organically sound hearts. In only two of the cases was the postural effect on the P-R interval studied, and in both there was a decrease similar to that in our Case 3, but it did not return to normal limits as in our Cases 1 and 2. After exercise and in a supine position two of the cases showed a P-R interval within normal limits while the third showed Wenckebach phenomenon with prolonged P-R interval. Atropine was given in only two cases and in both instances abolished the A-V block.

TABLE II. A COMPARATIVE STUDY OF CHANGES IN P-R INTERVAL IN THE THREE CASES REPORTED IN THE LITERATURE

	POEL ²	LEVY ⁵	ALEXANDER AND BAUERLEIN ¹
AGE (YRS.)	15	14	64
SUPINE	Heart rate, 81. P-R interval 0.36 second	Heart rate, 86. Control P-R interval 0.26 second. Position not given	Heart rate: auricular, 62; ventricular, 35.5. P-R intervals increasing progressively from 0.2 to 0.4 second
STANDING	Heart rate, 74. P-R interval 0.30 second		Heart rate: auricular, 71; ventricular, 71. P-R interval 0.28 second
WENCKEBACH PHENOMENON	Absent	Present	Present
ATROPINE	Not given	A-V block abolished	Heart rate: auricular, 80; ventricular, 80. P-R interval 0.24 second
CAROTID SINUS PRESSURE	-	Not given	Not given
EYEBALL PRESSURE	-	-	-
EXERCISE	Heart rate, 90. P-R interval 0.18 second	Heart rate, 86. P-R interval 0.18 second	Heart rate: auricular, 80; ventricular, 75. P-R interval 0.22 to 0.32 second

SUMMARY

1. Two cases are presented to show that first and second degree heart block can be produced by change in posture from the upright to the supine.

2. The data show that in two of our cases a decrease of P-R interval will occur with change in posture but without a concomitant change in rate (Table I).

3. The effects of atropine, exercise, and carotid sinus and eyeball pressure have been studied in these cases.

4. A review of the literature and comparison with our cases has been made.

5. It is suggested that all cases of incomplete heart block be studied for postural evaluation.

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Clinical Reports

UNUSUAL PRIMARY LEIOMYOSARCOMA OF THE HEART

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P RIMARY tumor of the heart is rare. The following case is reported not only because of its interest as a case of leiomyosarcoma primary in the heart, but also for the reason that we feel the many observations and recordings contained within this protocol will be of value to clinicians in making a differential diagnosis between tumor of the heart and ventricular aneurysm following myocardial infarction. This case was erroneously diagnosed clinically as the latter. We were fortunate enough to have been given the opportunity of following this patient from a point very early in the course of his disease to the autopsy table, a period of approximately four and one-half months.

CASE REPORT

The patient, a 34-year-old white man, was first admitted to the Station Hospital, Fort Ord, California, on April 16, 1943, complaining of sharp, stabbing pain in the left upper abdomen; this pain was of approximately four weeks' duration. His general appearance at this time was good, although he was admitted to the ward in a wheel chair.

His past and family histories were irrelevant. In his personal history he admitted to the moderate use of tobacco.

His present illness began on March 20, 1943, while the soldier was on a scheduled 25-mile hike. After completing about 5 miles of the hike he was overtaken by a "choking up" sensation and had to fall out. He had no actual substernal pain but experienced a sensation as if he had "run a great distance."

For three days following, his temperature was 100° F., and on March 24, 1943, he was admitted to the Station Hospital, Camp McQuaide, California, where a diagnosis of pericarditis was made. A pericardial friction rub was heard at the time of admission and persisted for a period of ten days. Admission laboratory data at Camp McQuaide consisted of the following: red blood cells, 4,230,000; white blood cells, 14,800, with a normal differential; and hemoglobin, 70 per cent. Temperature returned to normal the day following admission to Camp McQuaide Hospital and remained normal thereafter. A chest roentgenogram taken April 8, 1943, revealed an enlarged left ventricle (Fig. 1, A and B). The white blood cell count at that time was 9,500, with a normal differential; red blood cell count, 4,850,000; and hemoglobin, 14.5 grams. His urine was normal; sedimentation rate was 19 mm. in one hour.

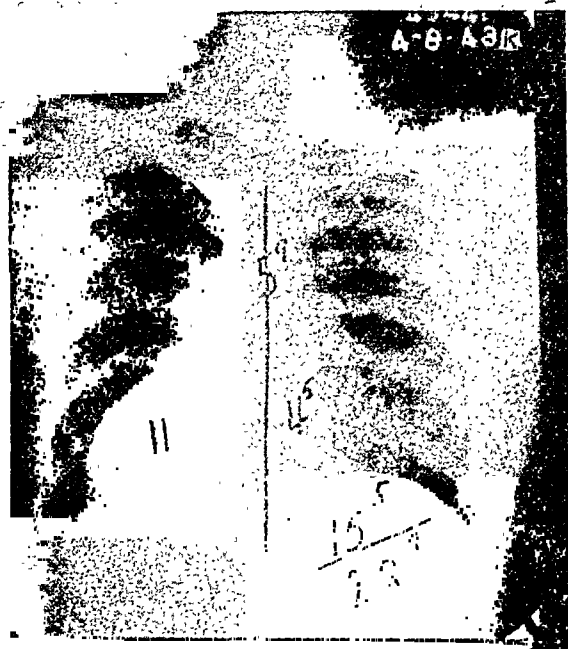
He was transferred to the Station Hospital, Fort Ord, California, on April 16, 1943. He was seen by the cardiologist who made an admitting provisional diagnosis of pericarditis subsequent to an acute arteritis with myocardial infarction. The electrocardiogram at the time of admission showed evidence of pericarditis with a possible myocardial infarction (Fig. 2). Physical examination at the time of admission was negative except as related to the heart.

The point of maximum intensity of the cardiac beat was in the fifth intercostal space just lateral to the nipple line. Heart sounds were of fair quality; no murmurs or friction rub was heard. The pulse rate was 80 per minute, and the blood pressure was 130/70. Initial treatment consisted largely of rest in bed.

Because of enlargement of the left ventricle noted on the roentgenograph of the chest taken April 8, 1943, fluoroscopic examination was done several days following admission to this hospital which revealed the enlargement of the heart to involve only the apical portion of the left ventricle. Pulsations were normal in all portions of the heart except in this region where they were seen to be extremely weak.

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By May 1, 1943, the sedimentation rate had returned to normal, and he was relatively asymptomatic. Despite repeated electrocardiograms showing evidence of persistent myocardial damage, the patient progressed in a relatively asymptomatic manner. A roentgenograph of the chest taken May 8, 1943, showed further enlargement of the left ventricle (Fig. 3). Repeat fluoroscopic study revealed very feeble pulsations of the entire left ventricle; this observation was corroborated by kymographic tracings. He was still asymptomatic but spent most of the time in bed or walking about the ward.



A.



B.

Fig. 1.—A, Posteroanterior 6-foot roentgenogram of the chest taken April 8, 1943, showing moderate enlargement of the left ventricle. B, Left anterior oblique 6-foot projection of the chest taken April 8, 1943, showing enlargement of heart to be confined to the region of the left ventricle.

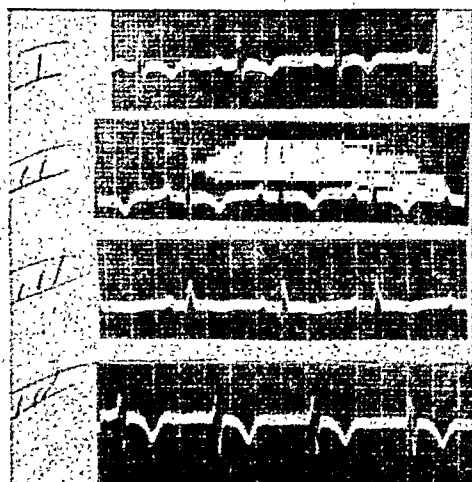


Fig. 2.

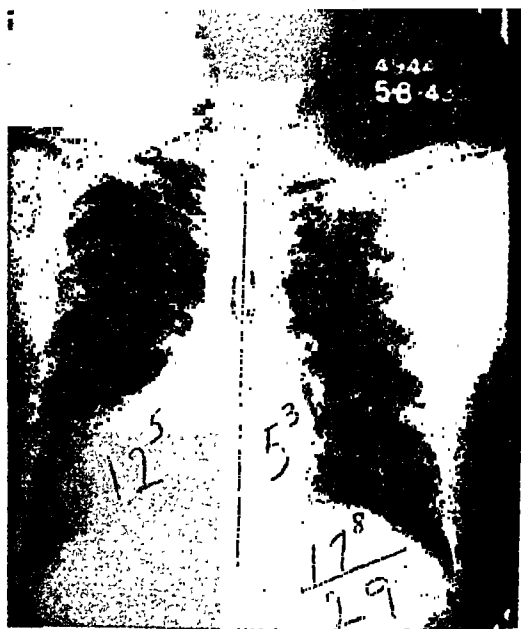


Fig. 3.

Fig. 2.—Electrocardiogram taken April 16, 1943, showing negativity of T waves in all leads with slight slurring of R. No RS-T elevation or depression but slight coving S-T. Lead IV standard IVF.

Fig. 3.—Posteroanterior 6-foot roentgenogram of the chest taken May 8, 1943, showing further enlargement of the left ventricle with the cardiac shadow beginning to show the so-called "boot shape."

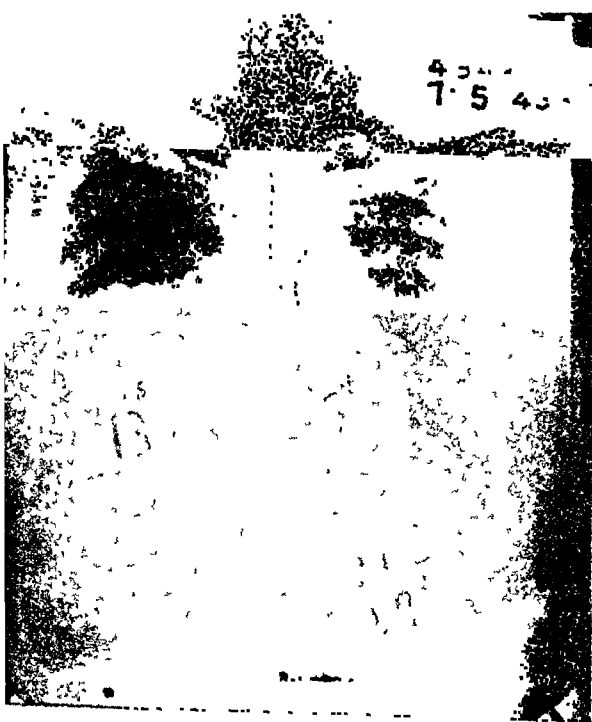
On June 4, 1943, his venous pressure was determined as 9 cm. (normal 3 to 8 cm.), and his circulation time was 17 seconds (normal 15 to 18 seconds).

On June 9, 1943, he first noted the appearance of orthopnea at nighttime which required the use of an extra pillow for comfortable sleeping. At this time there was noted a short, sharp, harsh, systolic, aortic murmur. The heart rate at this time was 100. The lungs were clear to auscultation, but a mild cardiac decompensation was apparent clinically. The heart murmurs were interpreted as being functional in nature and due to cardiac dilatation.

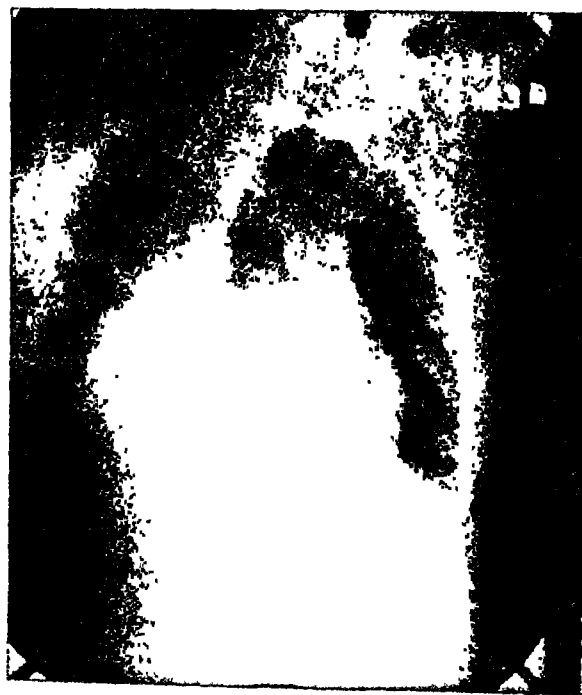
Roentgenographs of the chest on this date revealed further enlargement of the heart, the left border of which reached the lateral chest wall; the total transverse diameter now measured 19.9 cm. (Fig. 4). The cardiac murmur persisted, and the pulse rate now reached



Fig. 4.—Posteroanterior 6-foot roentgenogram of the chest taken June 9, 1943, showing still further enlargement of the left ventricle area, the left border of the heart touching the lateral wall of the thorax. Also there is beginning enlargement towards the right.



A.



B.

Fig. 5.—A, Posteroanterior 6-foot roentgenogram of chest taken July 5, 1943, showing even greater enlargement of the heart. The mediastinum appears displaced slightly toward the right. The heart has assumed the "boot shape." B, Left anterior oblique 6-foot projection taken July 5, 1943, showing the enlargement of the heart to be confined apparently to the left ventricle.

108 beats per minute. His venous pressure on June 12, 1943, was 13.5 cm., and his circulation time had increased to 31.2 seconds.

By June 16, 1943, his cardiac decompensation was greater with the presence of a moderate amount of dependent pitting edema. Digitalization was instituted following which his pulse rate dropped to 84 beats per minute. His orthopnea, however, remained, and the total transverse diameter of the heart now increased to 20.6 centimeters. Soon following, it was noticed that he was beginning to have what appeared to be an icteric tinge to his sclerae, but an icterus index revealed only 7.5 units of bilirubin.

By June 28, 1943, his decompensation had improved somewhat, although his peripheral edema persisted, and he had but slight difficulty in breathing at nighttime. Blood counts at this time revealed his red blood cell count to be 3,820,000 and his hemoglobin to be 10.5 Gm., as compared to an admission red blood cell count of 4,580,000 and a hemoglobin of 14.5 grams. His urine, which on admission had been entirely normal, now contained 3 plus to 4 plus albumin, an occasional pus cell, and a few casts of all types. His general condition appeared worse.

On July 5, 1943, radiographs of the chest revealed the left border of the heart to extend completely to the lateral wall of the chest with apparent displacement of the heart to the right, including the lower end of the trachea and right main bronchus (Fig. 5, A and B). There had also occurred some increase upward in the position of the left border of the heart so that its left upper border lay transversely, producing a so-called boot-shaped appearance of the heart. The total transverse diameter of the heart was 21.9 centimeters. Several days later his decompensation became severe with a marked pitting edema of both lower extremities with a large amount of fluid in the peritoneal cavity.

On July 2, 1943, his total serum proteins were found to be 6.5 Gm., with 4.1 Gm. of albumin and 2.4 Gm. of globulin per 100 cubic centimeters.

With the use of diuretic drugs the patient excreted large amounts of fluid, but, despite this, his edema failed to improve.

Early in August his liver and spleen became quite tender and his icterus index rose to 159 units.

His general condition rapidly became critical, and on Aug. 6, 1943, he was conscious only for short periods of time; he expired on Aug. 7, 1943. The final clinical diagnosis was: massive aneurysmal dilatation, left ventricle, probably on the basis of myocardial infarction, with subsequent myocardial failure.

Autopsy Findings.—(For the sake of brevity only those findings considered to be significant are given.) The skin and sclerae were icteric, and there was pitting edema of the lower extremities.

A. Gross: Upon removal of the sternum and ribs, an extremely enlarged heart was encountered. The left border of the heart was in contact with the lateral thoracic wall. The enlargement had been to such an extent that approximately 85 per cent of the left pleural cavity was occupied by heart and tumor mass. There was also enlargement to the right so that the heart occupied approximately 35 per cent of the right pleural cavity.

The left lung was completely collapsed, had been markedly displaced posteriorly and superiorly, and was bound down by firm fibrous adhesions over the apical half. The right pleural cavity contained 750 c.c. of thin, yellowish-brown, cloudy fluid. The right lung was 75 per cent collapsed, and its surface, particularly in the lower half, was covered by yellowish-red fibrinous exudate.

The arch of the aorta was displaced superiorly.

The heart and lungs together weighed 2,960 grams, of which the lungs made up an estimated 450 grams (Fig. 6). The enlargement of the heart involved primarily the left ventricle. It extended about halfway around the heart by intrapericardial growth "encuirasse." The cavity of the left ventricle was considerably decreased in size, measuring 3.5 cm. from the aortic valve to apex. In the apex of the ventricle were two polypoid masses which projected into the cavity, further reducing its size. The cavity of the right ventricle was also somewhat decreased in its capacity, although less so than the left, and measured 4.5 cm. from the pulmonary valve to the apex. The chordae tendeneae were shortened, and the papillary muscles were somewhat hypertrophied. The hypertrophy of the right ventricular wall was particularly marked. This ventricle was also displaced upward, but was not invaded.

The endocardium throughout all chambers of the heart was smooth and glistening. There was no lesion of any of the valve leaflets. The valve rings were of their usual size, except for the aortic which had been mildly compressed by a large mass of tumor tissue, 4.5 by 2.2 cm., which was exactly similar to that which is described subsequently. This mass of tumor



Fig. 6.—Over-all appearance of the entire intrathoracic mass. (U. S. Army Medical Museum, Reg. No. 76862.)

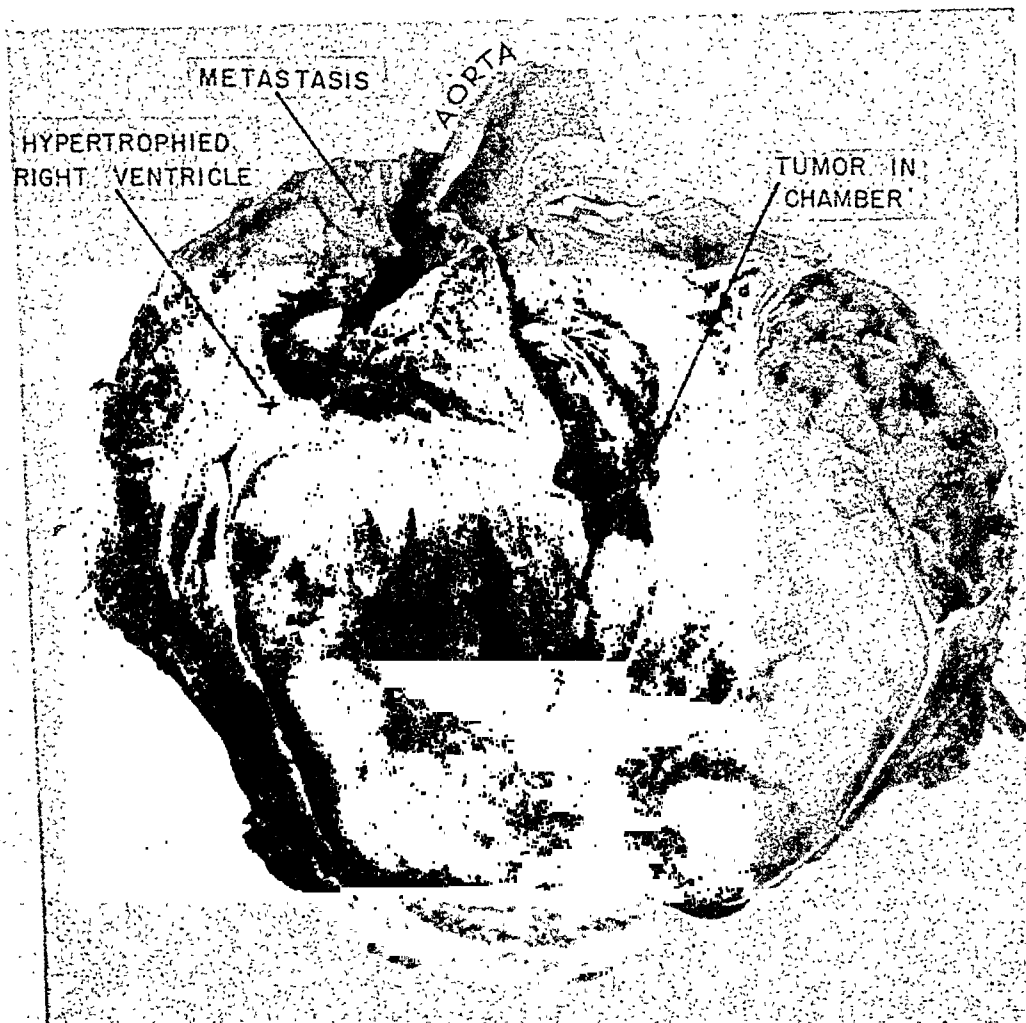


Fig. 7.—Tumor mass and heart opened to reveal the various features of the two. (U. S. Army Medical Museum Reg. No. 77304.)

tissue had also produced some compression of the superior vena cava as it entered the right auricle. One end of this mass lay upon but did not compress the pulmonary artery. This periaortic mass was entirely extra myocardial and extended upward from the auriculo-ventricular groove. It was in no way connected with the main tumor and was considered to be an intrapericardial metastasis.

Projecting from the apex of the heart was a large tumor mass which, from the inferior border of identifiable myocardium to the tip of the mass, measured 10 centimeters. This mass was composed of moderately firm, yellowish, tumor tissue, contained in which were several large areas of degeneration, the largest of which measured 4 cm. in diameter, and was centrally placed. Throughout the tumor mass were irregularly shaped strands of reddish-brown tissue which appeared to be degenerating myocardium. The line of demarcation between the tumor and the heart muscle was rather sharp (Fig. 7).

The tumor tissue itself occurred in ill-defined strands and whorls, some strands of which were paler and more dense than others. Upon sectioning, the tumor tissue swelled up and overhung the pericardium. Despite careful search, the exact site of origin of the mass could not be determined, although from its location it is safe to say that it probably was in or near the apex of the left ventricle.

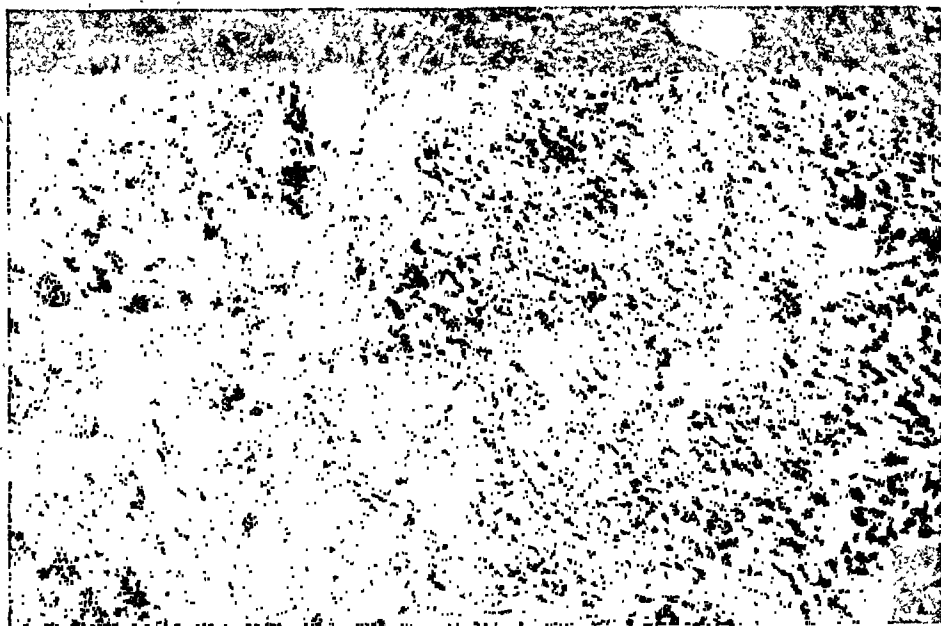


Fig. 8.—Photomicrograph showing encroachment on and isolation of myocardial cells by the neoplastic cells. (U. S. Army Medical Museum, Reg. No. 76432.) $\times 435$.

The tumor mass had stretched the overlying visceral pericardium and was attached to it. This portion of the pericardium was somewhat thickened, averaging 0.15 centimeters. However, it could be dissected from the underlying tumor tissue without much difficulty. The pericardial space was completely obliterated, and the two layers of the pericardium could be separated only by sharp dissection. The parietal pericardium was thickened and averaged 0.2 centimeters. Neither layer of the pericardium showed any gross involvement by the tumor.

The peritoneal cavity contained 2,300 c.c. of thin, yellowish-brown, slightly cloudy fluid.

The duodenum contained three large ulcer craters, which were agonal in type.

Both the cystic and common bile ducts were occluded by enlarged, homogeneous appearing lymph nodes at points 1 cm. from the hepatic duct junction and 1.5 cm. distal to this junction.

The remaining abdominal organs revealed only a considerable degree of passive congestion.

Thorough examination of the brain failed to reveal any gross lesion.

B. Microscopic: The microscopic description for the purpose of this report is limited to the findings as they pertain to the heart and the tumor mass. Those sections of the myocardium taken away from the tumor mass revealed the muscle cells to be normal in their appearance although there were reactive changes in the myocardium with increased interstitial

tissue and a scattering of large mononuclear and other cells. The interstitial blood vessels were entirely normal.

The pericardium was moderately thickened and in some areas was slightly increased in its cellularity. Scattered diffusely through some areas of the pericardium were collections of lymphocytes.

The endocardium was not thickened in any area.

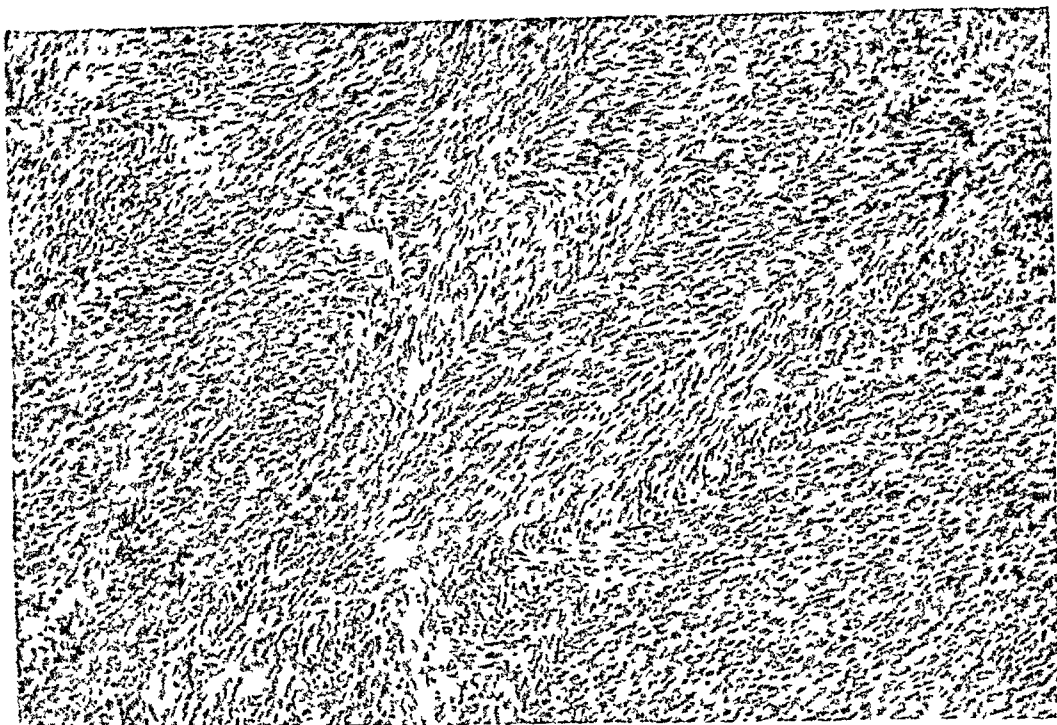


Fig. 9.—Photomicrograph revealing the cellular arrangement of the tumor. (U. S. Army Medical Museum. Reg. Nos. 77247, 77250.) $\times 165$.

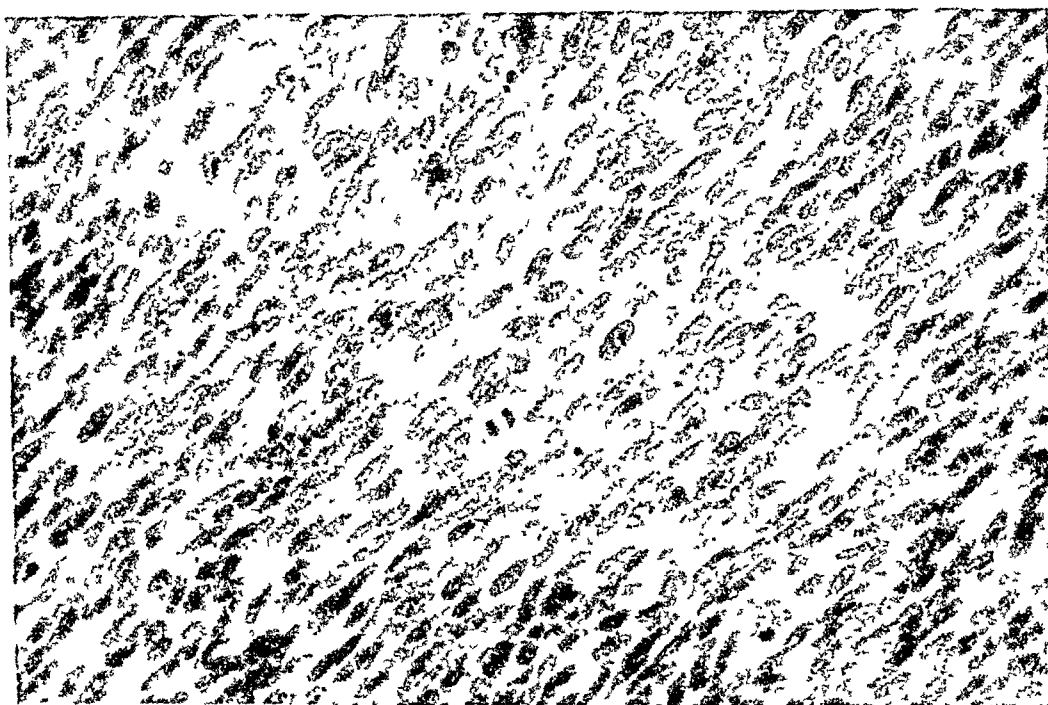


Fig. 10.—Photomicrograph revealing nuclear detail. Note arrangement of chromatin and mitotic figure. (U. S. Army Medical Museum, Reg. No. 77245.) $\times 640$.

Sections taken from the line of juncture between the myocardium and the tumor mass revealed the latter to be encroaching upon the myocardial cells. Strands of the myocardium, as well as individual cells, were found deep within the tumor mass itself. These myocardial cells appeared as islands, having been isolated by the advancing tumor, and revealed varying degrees of degeneration (Fig. 8). In other areas there was a fairly sharp line of demarcation between the myocardium and tumor, and here a few strands of fibrous connective tissue formed a thin capsule between the two structures.

That portion of the tumor mass occurring closest to the myocardium was, by comparison with that elsewhere in the mass, much more cellular and of a higher degree of malignancy.

Sections from the bulk of the tumor mass were highly cellular; these cells occurred in whorls and bands projecting in all directions without any apparent attempt at reproduction of a specific architectural picture. The density of the tissue varied considerably from one area to the next. The individual cells of the tumor were not particularly large and were composed almost entirely of nuclear material. Cytoplasmic elements in some areas were indistinguishable; in others, however, varying amounts of cytoplasm could be made out. Where it could be made out, the cells were spindle shaped with pointed ends. No blue fibrils were found in the phosphotungstic acid hematoxylin preparations, although Wilder reticulum stains brought out some reticular fibers in relation to the cells. The nuclei were moderately chromatic; the chromatin was most dense around the periphery of the nucleus and accumulated throughout the remainder of this structure in dots of varying size with some arrangement in a vague linear fashion perpendicular to the long axis. Nucleoli were not common. There were occasionally as many as two mitotic figures per high power field (Figs. 9 and 10).

In many areas the tumor more or less suddenly differentiated itself from immature cells to a more mature type of cell which in all of its appearance and staining reactions was fibrous connective tissue. In these more mature areas the nuclei were more elongated, more compact, and the cytoplasm was more abundant. The area of degeneration described in the central portion of the tumor mass was found to be typical of the myxomatous type.

The polypoid tumor mass in the left ventricle was made up of tumor cells of the same type as previously described, which were collected largely in the base of the polyp itself. Towards the periphery of the polyp there was gradual differentiation through various stages to adult connective tissue which made up the enveloping capsule of the polyp itself. This differentiation was splendidly brought out by Masson's stains.

Sections of the mass which surrounded the base of the aorta were composed of neoplastic cells exactly similar in type to those already described.

The enlargement of the lymph nodes surrounding the biliary tract was found to be due to simple hyperplasia and early fibrosis, probably related to stasis.

COMMENT

As can be noted from the above protocol, the correct ante-mortem diagnosis was not made in this case. However, we wish to state that the presence of a cardiac tumor was mentioned as a possibility by many who observed this patient during the course of his illness. But no one thought the tumor possibility as being the most likely diagnosis.

The original electrocardiographic changes are those that may be seen in an infarction as well as in pericarditis without infarction. Because of the history of a choking sensation while the deceased was on a hike, the onset of which was sudden, followed by a pericardial friction rub and slight fever the next day, with associated electrocardiographic changes that were compatible with an early infarction, we concluded that the enlargement of the left ventricle seen on the roentgenogram of April 8, 1943, could easily be explained; namely, upon the basis of aneurysmal dilatation. The fluoroscopic examination performed on April 11, 1943, showed that the enlargement of the heart was limited to the apical portion of the left ventricle at which site weak pulsations were discerned.

The nonclearing of the electrocardiographic abnormalities over a period of several months (Figs. 11, 12, and 13) without clinical evidence of secondary infarctions was a bit disconcerting and failed to substantiate our impression of aneurysm incident to myocardial infarction. But then, later, the radiographic and kymographic findings of a boot-shaped appearing heart shadow and absent pulsations in the left ventricle gave us evidence that we thought was incontrovertible, and so we assumed that we were dealing with a rapidly stretching myomalacic left ventricle, which subsequently failed, terminating in the death of the patient.

The absence of paradoxical pulsations of the left ventricle upon fluoroscopic study did not alter our opinion of aneurysm, as we explained the lack of such pulsations upon the basis of a mural thrombus situated on the endocardial wall of the supposedly infarcted left ventricle. This thrombus was believed to be large enough to prevent any outward bulge during systole.

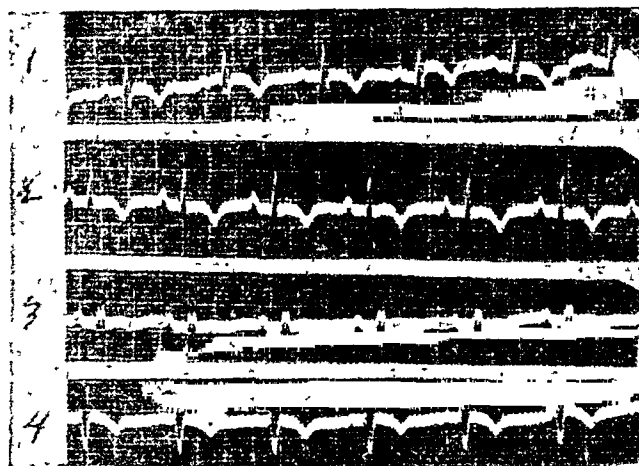


Fig. 11.—Electrocardiogram taken June 8, 1943, showing same degree of negativity of T waves in all leads. There is notching of R_2 and absent R_4 . No RS-T elevation or depression but slight coving S-T₁ and S-T₂. Lead IV standard IVF.

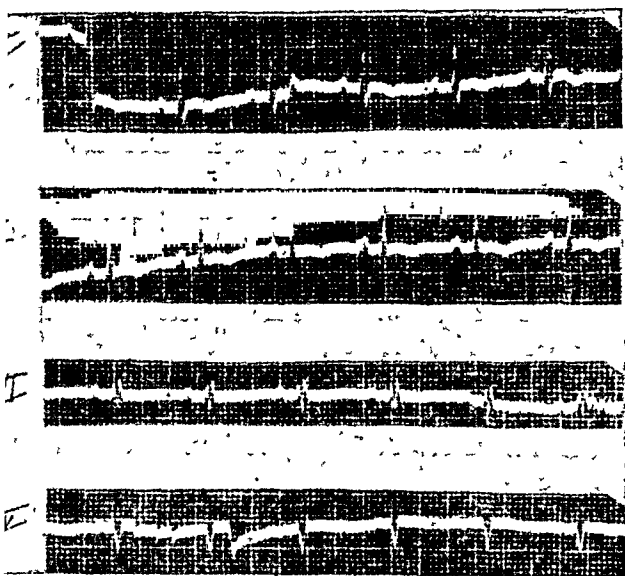


Fig. 12.

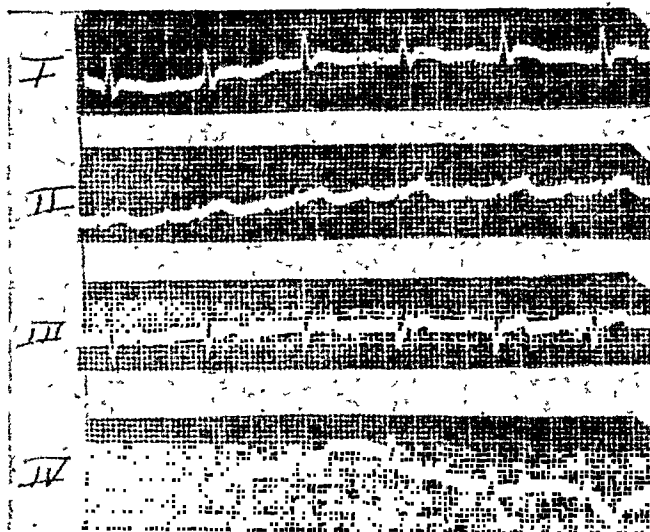


Fig. 13.

Fig. 12.—Electrocardiogram taken June 29, 1943, showing tendency toward left axis deviation. T_1 and T_2 are only slightly elevated now. T_3 and T_4 are isoelectric. R_4 is still absent. Still slight coving S-T₁ and S-T₂. Lead IV standard IVF.

Fig. 13.—Electrocardiogram obtained Aug. 7, 1943, showing low voltage QRS complexes all leads. T_1 and T_2 now are diphasic. T_3 is upright. T_4 is diphasic. R_4 is slurred. Slight elevation of S-T₁. Lead IV standard IVF.

However, in retrospect, we feel that there are certain findings that should have enabled us to differentially exclude aneurysm. In the first place, the presence of a friction rub for a period of ten days is unusual in a case of simple single infarction. Then, too, there was no blood pressure drop as is often seen in infarction of the left ventricle. In addition, the electrocardiographic changes were not typical of infarction in that originally all T waves were inverted with never any elevation or depression of the S-T segments, only slight coving. Later there was seen some notching of the QRS components which, in the absence of such notching during the two or more months following the onset of the supposed infarction, would point toward progressive myocardial pathology of some

type. In the absence of clinical or other laboratory evidence to support secondary infarction to account for the progressive nature of the electrocardiographic findings, the diagnosis of a tumor should have been more strongly entertained. Furthermore, the rapid enlargement of the heart should have aroused our suspicion more than it did, in favoring a diagnosis of tumor. This latter observation coupled with the relatively rapid course favored a tumor diagnosis rather than one of aneurysmal dilatation.

The autopsy findings are remarkable because of the single site of location of the tumor with only a single intrapericardial metastasis. Despite careful gross and microscopic examination of all tissues no evidence of distant metastases of any type could be discovered. This is felt to be significant because clinically the exitus was mechanical in type rather than due to late stages of malignancy. The microscopic examination, as noted, revealed a spindle-cell type of growth.

From the various staining procedures carried out, two main possibilities present themselves, namely fibrosarcoma and leiomyosarcoma; the latter is comparable to the rare pleural tumors.

The exact site of origin of the tumor cannot be postulated exactly, either from a gross or a microscopic standpoint. We are of the opinion that it started in or near the apex of the left ventricle and perhaps the pericardium. The occurrence of an isolated tumor mass at the base of the heart in the area of the ring of the aortic valve is interesting. As noted in the description, this mass had absolutely no connection with the main tumor mass, and it is felt that this represents an area of metastasis to the heart itself. The possibility of simultaneous origin of the two masses is considered but discarded because of insufficient evidence upon which to base such a conclusion.

Taking all of the gross and microscopic features into account, it is concluded that this is a leiomyosarcoma, while an alternative choice of fibrosarcoma is also suggested.

PRIMARY ALVEOLAR CELL CARCINOMA OF THE LUNG WITH PULMONARY ARTERY SCLEROSIS AND RIGHT HEART FAILURE

CASE REPORT

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THE coexistence of pulmonary neoplasms and pulmonary arteriosclerosis is rare. In a recent review of the pathology of the vessels of the pulmonary circulation Brenner¹ found but one such case in his series of one hundred patients and gathered four others from the literature. We are reporting an additional case which is interesting because of the association of advanced atherosclerosis of the pulmonary arteries and cor pulmonale with a diffuse alveolar cell carcinoma of the right lung in a young woman.

REPORT OF A CASE

R. W., a 20-year-old college girl, was told she had a "spot" on her right lung in 1939 after a routine roentgenogram of her chest had been made. The heart silhouette at that time was normal. Because of her apparent good health the finding was disregarded. Two tuberculin tests were negative.

During June, 1940, she complained of pain in the right side of the chest which was diagnosed as right basal pneumonia with pleurisy. A moderately productive cough without hemoptysis appeared and persisted for three weeks. The cough and pain in the right side then became less intense and was present when she was admitted to the hospital on Feb. 2, 1941. She stated that she had lost 4 pounds in the month before admission.

She was in good physical condition when first examined. Percussion dullness and exaggerated breath sounds were present over the right lung base. The heart sounds were regular, and aside from accentuation of the second pulmonic sound no changes were apparent. The liver edge could not be palpated.

A chest teleroentgenogram revealed a uniform opacity extending obliquely from the right lung root to the diaphragm obscuring the right heart border. The main trunk of the pulmonary artery was prominent. At first the possibility of a congenital heart lesion was considered, but a review of the film taken in 1939 made it clear that the pulmonary artery prominence had developed since that time.

The blood Kline reaction was normal. A blood count revealed her hemoglobin to be 107 per cent, with 5.5 million red cells, 13,300 white cells, and a normal differential count.

Bronchoscopic examination revealed slight narrowing of her right lower bronchus with chronic inflammatory changes. A biopsy was reported as chronic inflammatory tissue. Iodized oil bronchography showed slight bronchiectatic changes in the lower lobe bronchi. The lumen of the trachea and main bronchi was normal.

On Nov. 25, 1941, she was readmitted because of fever, chills, and a hard cough productive of thick, green, mucoid sputum. She appeared malnourished, her lips were cyanotic, and her fingers were clubbed. There was dyspnea on slight exertion, and edema was present over the sacrum and ankles. A flat percussion note, increased tactile fremitus, and bronchial breathing were present over the right base posteriorly. Many moist and dry fine râles were heard over the entire chest. The heart rhythm was regular, and the sounds were not unusual except for an accentuated second pulmonic sound. The liver could now be felt 4 finger-breadths below the costal margin.

Teleroentgenographic examination of the chest showed the right lung opacity to be more extensive than it was previously, obliterating the right costophrenic sinus. Her heart was

displaced toward the left, and there was marked prominence and increased amplitude of pulsation of the main trunk of the pulmonary artery.

Bronchoscopic examination again revealed the chronic inflammatory changes in the right lower bronchus. Electrocardiographic examination showed right axis deviation and changes in the main ventricular complexes due to myocardial changes. Her venous pressure was 130 mm. of water, the saccharin circulation time was 25.5 seconds, and the ether circulation time was 16.5 seconds.

The patient grew progressively worse during the next few weeks. Cyanosis increased markedly, and the dyspnea and orthopnea became more pronounced. About 50 c.c. of mucopurulent sputum were expectorated daily. The peripheral edema was not relieved by vigorous attempts to induce diuresis.

An exploratory thoracotomy for a possible lung tumor, performed five weeks after admission, revealed an inoperable mass involving the right lower lobe and extending into the upper lobe. The patient expired eighteen hours after operation in advanced heart failure.



A.

B.

Fig. 1.—A, Teleroentgenogram showing opacity in right lung base and paracardiac region. The heart is shifted toward the left. The main trunk of the pulmonary artery is prominent. B, Right anterior oblique projection showing dilatation of the main trunk of the pulmonary artery and prominence of the conus of the right ventricle.

The following are the significant observations made at post-mortem examination. Her right lung weighed 780 grams, and her left lung weighed 240 grams. The right lung was firm, rubbery in consistency throughout except at its apex, and presented deep red-grey surfaces on cut section. At first glance the possibility of a pneumonic consolidation was considered. No necrotic foci were seen. The trachea and main bronchi were normal throughout. The left lung revealed a few circumscribed nodules in the lower lobe which proved to be metastatic.

The main trunk of the pulmonary artery presented numerous grey-yellow atheromatous plaques which rendered the vessel almost rigid. The atherosclerosis extended into the lesser branches of the pulmonary arteries in both lungs so that they projected well above the cut surfaces.

The heart weighed 315 grams. The right ventricle was markedly thickened, measuring 1.2 centimeters. The left ventricle was 1.4 cm. thick. The coronary arteries were patent and contained occasional small yellow atheromatous plaques. The myocardium and valves were normal.



Fig. 3.—Photograph of the heart showing hypertrophy of the right ventricle.



Fig. 2.—Photograph of the right lung showing diffuse carcinoma and pulmonary artery sclerosis.

On microscopic examination the right lung parenchyma was diffusely infiltrated with tumor cells which filled the alveoli and extended into the bronchi and bronchioles. The stroma of the tumor was made up of the alveolar walls. The alveolar structures which remained in the diffuse sheet of tumor cells existed as incomplete single layers of large cuboidal cells with large hyperchromatic nuclei. The tumor cells were large, either round or polygonal in shape, and had large or vesicular deeply-staining nuclei. Mitotic figures were rare.

There was marked thickening of the walls of the arteries and arterioles with intimal proliferation which resulted in considerable narrowing of the lumina of the smaller vessels. No such changes were noted in the smaller vessels of the kidneys, liver, or heart.

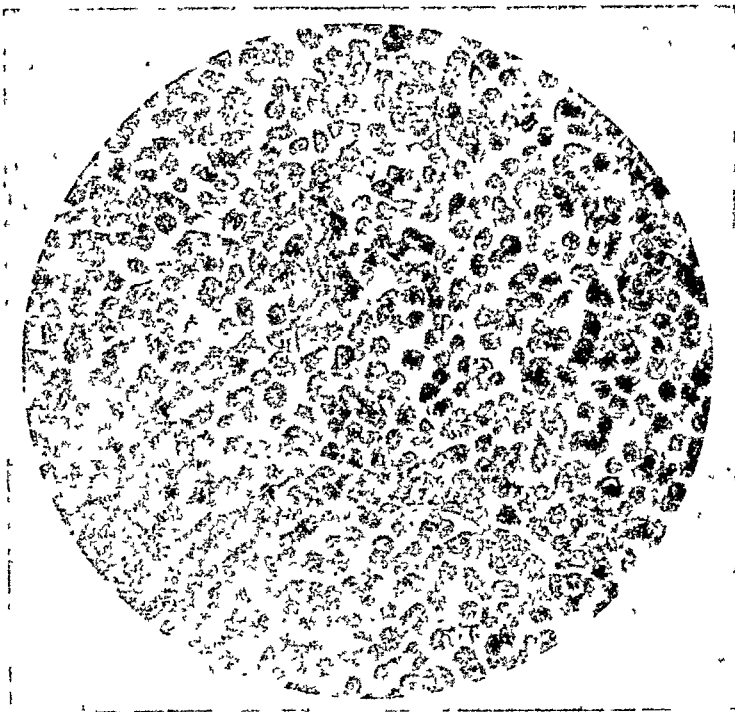


Fig. 4.—Photomicrograph showing the tumor cells (hematoxylin and eosin stain; magnification, $\times 400$).



Fig. 5.—Photomicrograph showing the thick-walled vessels with narrowed lumina (hematoxylin and eosin stain; magnification, $\times 150$).

COMMENT

Pulmonary arteriosclerosis is usually divided into "primary" and "secondary" groups. The former refers to those for which no cause for pulmonary hypertension can be found and is usually accompanied by right ventricular hypertrophy. Cases sometimes referred to as senile in origin fall into this group even though there is neither right ventricular hypertrophy nor any obvious cause for the pulmonary hypertension.

Secondary pulmonary arteriosclerosis is the designation applied to the larger group in whom some obvious pulmonary or cardiac cause for the increased pulmonary arterial pressure exists. Among these are heart disease, particularly mitral stenosis, chronic heart failure, and chronic lung conditions such as bronchiectasis, emphysema, tuberculosis, lung abscess, and extraluminal compression of the pulmonary artery.

In 1942, Neuberger and Geever² reported the pathologic findings in twenty-five cases of alveolar cell carcinoma of the lung gathered from the available literature. In none of these was there any mention of pulmonary arteriosclerosis. Brenner was unable to ascribe any relationship between the lung tumor and pulmonary arteriosclerosis in the five cases he mentioned.

The ultimate cause of the pulmonary hypertension could not be ascertained in our patient. It might be more than coincidental that the pulmonary arteriosclerosis and the alveolar cell carcinoma of the right lung were present together. The fact that the pulmonary artery dilatation and the cor pulmonale appeared after the first x-ray examination of the chest in 1939 suggests that perhaps some relationship may have existed between the pulmonary artery sclerosis and the tumor.

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1. Brenner, O.: Pathology of the Vessels of the Pulmonary Circulation, Arch. Int. Med. 56: 211, 1935.
2. Neuberger, K. T., and Geever, E. F.: Alveolar Cell Tumor of the Human Lung, Arch. Path. 33: 551, 1942.

Abstracts and Reviews

Selected Abstracts

Rosenblueth, P. A., and Ramos, J. G.: The Interpretation of the Electrogram of the Cardiac Ventricle. Arch. Inst. Cardiol. Mex. 14: 232, 1945.

The electric phenomena of the cardiac ventricles of cats and dogs were recorded by means of a cathode-ray oscillograph and the following observations were made.

When the leads are applied directly to two intact regions of the muscle, a typical diphasic electrogram is obtained. If an extensive injury (ligature or burn) is made between the leads, the records are not modified, although the response recorded from the injury to either of these two intact regions tested originally are typically monophasic.

The existence of an injured region can only be appreciated in records taken from a direct to a distant lead if the direct lead is in contact with the damaged tissue. If, instead of being applied directly, the near electrode is placed on a layer of cotton moistened with Ringer's solution which covers the heart, so that the lead becomes diffuse and makes contact with both injured and intact tissue, then the existence of an injury can be appreciated in the records even when the electrode is moved over a relatively large area in front of the heart.

The polarization with direct current of either of the two lead-off regions results in marked changes of the diphasic electrograms. Applications of direct current to other regions of the heart, including the zone intermediate to the leads, do not modify the electrograms. Similarly, the monophasic records are strikingly modified when the live lead-off region is polarized anodally or cathodally, but are unchanged by the application of direct current to the intermediate zones or to the injured region.

From these data the following inferences are drawn. (a) The only regions in the ventricle that contribute significantly to the electrograms obtained with leads applied on the surface are those in direct contact with the leads; the electrical phenomena which occur in other regions, including those intermediate to the leads, contribute only minimally or do not contribute to the electrograms. (b) There are no potential changes at an injured region concomitant with the activity of the heart. (c) The monophasic electrograms, therefore, show only the potential changes which take place at the intact region which is in contact with the corresponding electrode; they may be designated as monotopic; the diphasic electrograms are ditopic since they correspond to the algebraic sum of the two monotopic responses. (d) When applications of direct current to the injured region do not modify the monophasic electrograms it may be concluded that the injury is complete for the purpose of the record, and it may be concluded, therefore, that the electrograms are strictly monotopic; these strictly monotopic records are not simple but complex, they exhibit several components which differ in amplitude, polarity, and time course. (e) The existence of a cardiac injury may be detected in the human electrocardiogram because the distant electrodes are prolonged by the conducting media of the organism and the real leads are diffuse and come in contact with the injury.

AUTHORS.

Alexander, R. S.: The Effects of Blood Flow and Anoxia on Spinal Cardiovascular Centers. Am. J. Physiol. 143: 698, 1945.

By employing the activity in the inferior cardiac nerve of the cat as a direct index of the activity in the sympathetic outflow to the cardiovascular system, the following conclusions have been reached:

After removal of all possible sources of reflex inhibition, a rise in thoracic blood pressure produced by injections of adrenalin or pitressin or by sudden occlusion of the abdominal aorta still serves to inhibit the tonic activity in the thoracic sympathetic outflow to the cardiovascular system.

The tonic activity arising within the spinal cardiovascular centers of deafferent spinal preparations is sensitive to changes in oxygen tension. This activity is depressed by hyperventilation or ventilation with a mixture of 90 per cent oxygen and 10 per cent carbon dioxide, and stimulated by asphyxiation or ventilation with pure nitrogen.

In the deafferent spinal preparation, a rise in blood pressure inhibits sympathetic activity by increasing the flow of blood to the spinal cord. This increases the supply of oxygen to the spinal cardiovascular centers and thus depresses their activity.

It is suggested that the oxygen tension in the spinal cord of the normal animal may contribute to the excitatory state of the spinal cardiovascular centers, and thereby reinforce the buffer reflexes which are integrated at higher levels of the nervous system.

AUTHOR.

Duomarco, J., Recrate, P., and Rimini, R.: Influence of Abdominal and Thoracic Pressure Upon the Venous Return in the Inferior Vena Cava. *Rev. argent. de cardiol.* 11: 286, 1945.

An artificial experimental model was devised in which the physical conditions which determine the venous return in the inferior vena cava were studied.

In the case of the inferior vena cava there is a phenomenon of venous collapse which makes it impossible for the variations of thoracic and abdominal pressure to influence directly the venous return.

The thoraco-abdominal pressure difference protects the abdominal venous system from any easy stagnation.

The pressure variations due to respiration may cooperate in the venous return only in certain conditions in which the inferior vena cava is distended.

AUTHORS.

Stead, E. A., Jr., Warren, J. V., Merrill, A. J., and Brannon, E. S.: The Cardiac Output in Male Subjects as Measured by the Technique of Right Atrial Catheterization. Normal Values With Observations on the Effect of Anxiety and Tilting. *J. Clin. Investigation* 24: 326, 1945.

Studies on the circulation were performed in twenty-two normal subjects in the basal state. Samples of mixed venous blood and measurements of the atrial pressure were obtained by inserting a catheter through the antecubital vein into the right atrium. The femoral arterial pressure was recorded optically by the method of Hamilton.

Nineteen experiments were carried out on eighteen subjects in whom the pulse rate was not above 82 beats per minute and in whom the metabolic rate did not exceed plus 10. The arteriovenous oxygen difference varied from 3.1 to 6.1 with an average of 4 volumes per cent. The cardiac index (liters per minute per square meter) ranged from 2.3 to 4.1, with an average of 3.3. The atrial pressure ranged from 0 to 85, with an average of 31 mm. of water.

Seven experiments were performed on five normal subjects in whom either the pulse rate exceeded 82 or the metabolic rate exceeded plus 10. These findings were interpreted as evidence of anxiety. The average arteriovenous oxygen difference was 3.1 volumes per cent. The cardiac index averaged 5.5, and the atrial pressure averaged 29 mm. of water. The increase in cardiac output was out of proportion to the increase in oxygen consumption. The rise in cardiac output occurred without any measurable change in atrial pressure.

When the subject was tilted to an angle of 70 degrees, the arteriovenous oxygen difference rose, and the cardiac output decreased. The average decrease in the cardiac index, when the subject was tilted, amounted to 23 per cent.

AUTHORS.

Neubauer, C.: Auricular Fibrillation and Auricular Flutter in Diphtheria. *Brit. Heart J.* 7: 59, 1945.

On clinical and bacteriologic grounds, the case was one of faucial diphtheria. Hemolytic streptococci are not uncommonly found in diphtheritic throat lesions caused by gravis strain, and in the case under discussion the presence of hemolytic streptococci, in addition to the development of a rash and strawberry tongue as described above, indicates beyond doubt a double infection. The persistent tachycardia and the diminished intensity of the first apical sound, the lowered blood pressure, and the increased blood sedimentation rate were clinical manifestations of a myocarditis. Auricular fibrillation, detected clinically and cardiograph-

ically three days later, confirmed the presence of myocarditis; it persisted for two days in spite of digitalis therapy and ultimately changed to auricular flutter. Anatomic and histologic findings at autopsy revealed an acute myocarditis with formation of ante-mortem mural thrombi.

Here, then, is an example of auricular fibrillation and auricular flutter developing as terminal events in the course of an extremely acute myocarditis.

AUTHOR.

Cookson, H.: Heart Block and the Simulation of Bundle Block in Diphtheria. Brit. Heart J. 7: 63, 1945.

Clinical and cardiographic findings are given of eight cases showing conduction changes among a series of eighty-three patients with diphtheria. Of four with latent block, a prolonged P-R interval has persisted in one for five months. Bundle branch block was observed in four unimmunized children, aged 12 years or less, and all died; complete block was recorded in one of these four. In two others bizarre ventricular complexes were found in association with a passive ectopic rhythm; at first sight these suggest a bundle branch lesion, but like the short P-R wide QRS syndrome, which seems a related condition, these changes do not appear to have any prognostic significance.

AUTHOR.

Pearson, R. S. B.: Sinus Bradycardia With Cardiac Asystole. Brit. Heart J. 7: 85, 1945.

A case of persistent sinus bradycardia with syncopal attacks due to cardiac standstill is described.

Evidence is given for believing that this is not vagal in origin but due to hypo-excitability of the pacemaker.

AUTHOR.

Costero, and Fuertes, G. A.: Frequency of Congenital Anatomic Lesions of the Heart in the City of Mexico. Arch. Inst. Cardiol. Mex. 14: 275, 1945.

In 1,000 consecutive autopsies with a complete pathologic study recorded in the Service of Pathology of the General Hospital of Mexico and carried out for Sept. 11, 1937, to Jan. 19, 1941, the frequency of congenital anatomic lesions of the heart and of the large vessels has been investigated with the following results:

1. Fenestration of the sigmoid valves was found in 253 cases. In 107 of them the lesion was of the pulmonary sigmoid; in 67, of the aortic sigmoid; and in 79, of the valves of both arteries. Of these cases 48 (18.97 per cent) coincided with other congenital abnormalities in the organism.

2. The foramen of Botal was incompletely closed in 179 cases, of which 80 (44.69 per cent) coincided with other congenital malformations.

3. The coronary arteries were abnormal in 36 cases; in 14 there were accessory coronaries; in eight there was duplicity in the opening of one of the coronaries; in two there were multiple openings; and in 12 the opening was displaced.

The following abnormalities were found only once.

4. Bivalve sigmoid, which coincided with other extracardiac congenital malformations.

5. Incomplete interauricular septum, coinciding also with other malformations.

6. Bifurcation of the apex, associated with fenestration of the sigmoid.

7. Dilatation of coronary sinus.

In 90 of the cases tabulated there were two simultaneous lesions, and, in five of them, there were three simultaneous congenital lesions of the cardiovascular system.

AUTHORS.

Grolnick, M., and Loewe, L.: Immunologic Studies in Patients With Subacute Bacterial Endocarditis Treated by Combined Penicillin-Heparin Method. J. Lab. & Clin. Med. 30: 559, 1945.

Twenty-seven patients receiving intensive and prolonged treatment with penicillin failed to develop any positive skin or ophthalmic reactions to a solution of penicillin containing 10,000 units per cubic centimeter. These patients did not develop any positive skin reactions to the source of this product, the mold *Penicillium notatum*.

From the present study penicillin would appear to be a very poor sensitizing agent.

AUTHORS.

Katz, L. N., Wise, W., and Jochim, K.: The Control of the Coronary Flow in the Denervated Isolated Heart and Heart-Lung Preparation of the Dog. *Am. J. Physiol.* 143: 479, 1945.

Coronary flow was studied in isolated heart and heart-lung preparations of dogs by examination and analysis of graphs correlating one or more factors with coronary flow in the control period at the start of each of seventy-nine experiments, and by data obtained in individual experiments following alteration of the various factors controlling the dynamics of the preparation.

In the graphs, coronary flow at the beginning of the experiments was found to vary with heart weight, but not with venous or aortic pressure levels. On the other hand, there was striking correlation of cardiac output (measured as pulmonary flow) with coronary flow, index of reciprocal of coronary resistance ($\frac{\text{coronary flow}}{\text{aortic pressure}}$), coronary flow per gram heart weight and $\frac{\text{coronary flow}}{\text{aortic pressure}}$ per gram heart weight. Correlations of work of the heart were similar to those of pulmonary flow since in our preparations the latter is the main variable in calculation of cardiac work. Coronary flow was found to be independent of aortic flow and of arterial oxygen level (of the range in our experiments) but coronary flow per gram heart weight tended to increase with increase of temperature or heart rate. The pressure drop between the aorta and right auricle in the heart-lung preparation correlated with aortic flow but not with coronary flow, indicating great variation in cross section of the coronary bed from preparation to preparation.

Examination of the course of individual experiments explained the above correlations and lack of correlations. They showed that the two most important mechanical factors influencing coronary flow in the isolated heart and heart-lung preparations, and presumably in the intact circulation, are cardiac output and systemic peripheral resistance—apart from spontaneous changes in coronary resistance which tend to occur during the course of the experiments. Thus, both increase in minute cardiac output and increase in extracoronary vascular resistance increase coronary flow.

These two factors act automatically and mechanically, without involving nerve reflexes or humoral mechanisms to bring about their effect. Their importance has hitherto not been properly appreciated.

Aortic pressure, which has an important influence on coronary flow in artificial preparations in which the coronary circuit is dissociated from the systemic circuit, does not play as important a part in the intact circulation. In the intact circulation, changes in aortic pressure are usually coincidental, secondary to change in cardiac output, systemic peripheral resistance, or both. The aortic pressure change tends to be minimized as a result of lessening of the change in total peripheral resistance by the alteration in coronary resistance brought about in turn by the passive alteration in the diameter of the coronary vessels. Change in coronary flow due to the predominant influence of one or both of the two factors mentioned above may occur in the absence of, or with similar or opposite, change in aortic pressure.

The degree of cardiac extravascular coronary compression is not as marked an influence as these other two factors, and its effect is obscured. Similarly the effect of cardiac output and peripheral resistance may mask or reverse the influence of nerve reflexes, drugs, and humoral substance on coronary caliber and coronary blood flow.

In experiments in which heart rate was deliberately altered there was no predictability in the change in coronary flow, since coronary flow changes occurred as the result of change in cardiac output or peripheral resistance, and no effect of heart rate per se could be distinguished.

The lack of relationship of coronary flow to aortic flow in the control periods of different preparations compared to the correlation of coronary flow with pulmonary flow, and the similar variability of aortic flow with respect to both coronary flow and pulmonary flow during the course of individual experiments, shows the fallacy in assuming, as some have done, that aortic flow below the mouths of the coronaries is an accurate index of either coronary flow, total cardiac output, cardiac work, or stroke volume.

AUTHORS.

Katz, L. N., Wise, W., and Jochim, K.: The Dynamics of the Non-Failure Period of the Isolated Heart and Heart-Lung Preparation. *Am. J. Physiol.* 143: 495, 1945.

In order to determine how many of the changes occurring in the course of heart failure are attributable directly to the loss of power of the heart, and how many represent spontaneous change or changes induced by manipulation, the constancy and interrelation of the

various pressures and flows in the period of little or no failure in thirteen isolated hearts and twenty-five heart-lung preparations are considered.

Improvement of the heart was frequently seen and manifested by a fall in venous pressure with constant cardiac output and work, or by an increase in cardiac output without rise in venous pressure. Improvement of the heart occurred early and apparently represented recovery from the initial manipulations in setting up the preparation; it also occurred later and in these cases, as in others, a common factor apparently was improvement in coronary flow.

In the course of a number of experiments a spontaneous decrease in coronary resistance led to increase in coronary flow, and, since the total peripheral resistance tended to decline, aortic pressure tended to fall. Usually peripheral resistance was adjusted to keep up aortic pressure. In a number of experiments the aortic pressure did not fall even though the systemic peripheral resistance was not adjusted. The probable explanation for this is discussed. The effects of spontaneous coronary dilatation upon the pulmonary arterial and the venous pressures varied and were actually determined by coincidental adjustments or changes. The spontaneous changes in coronary flow could not be correlated with variations in arterial oxygen content; apparently anoxemia of a degree sufficient to affect coronary flow was not encountered in these experiments.

Almost all the spontaneous changes in heart rate were related to temperature change and averaged about 10 beats per minute per degree centigrade. No correlation between heart rate and right venous pressure levels could be established.

Deliberate changes in cardiac output were accompanied by a like change in one or both venous pressures. In the heart-lung preparation the right venous pressure change was greater and more frequent than left. In the isolated heart preparation the left venous pressure rise was more frequent and greater than the right. Aortic pressure tended to rise but not in all cases. The cause for these changes is discussed.

When changes in the artificial systemic resistance did not change the aortic pressure, change in the other pressures was usually minimal or absent. When the aortic pressure was elevated by this procedure left venous pressure usually rose. A rise was seen less frequently and to a lesser extent in the pulmonary arterial and right venous pressures. Contrary effects of the increase in peripheral resistance operating downstream sometimes neutralized or reversed the pressure changes on the right side of the heart. Increase in artificial aortic resistance operated to raise the pressures upstream and lower them downstream.

Alteration in the pulmonary resistance in the isolated heart preparation caused changes in the same direction in pulmonary arterial pressure, right venous pressure, and, usually, aortic pressure.

Apart from the effect of secondary adjustments when the heart rate was changed, increase or decrease in heart rate beyond the optimum for adequate filling decreased the cardiac output. Arterial pressures tended to fall and venous pressure to rise, and the rise in venous pressures was accentuated by adjustments in peripheral resistances to maintain the arterial pressures.

The development of pulmonary edema, but not the plugging up of minor vessels by thrombi (both rare phenomena), increased the pulmonary resistance, increased the pulmonary arterial to venous pressure drop, and led to an increase in right venous pressure.

Spontaneous decreases in pulmonary resistance in the heart-lung, usually associated with simultaneous decrease in coronary resistance, decreased the pressure drop from pulmonary artery to vein and were usually reflected also in a fall in right venous pressure. Increase in the pulmonary flow by distending the lung blood vessels in the heart-lung tended to lessen the expected increase in the pressure drop between the pulmonary artery and veins.

AUTHORS.

Nylin, G.: Blood Volume Determinations With Radioactive Phosphorus. *Brit. Heart J.* 7: 81, 1945.

By the application of a new method worked out by Hevesy and his co-workers, employing blood corpuscles labeled with radioactive phosphorus, the circulating blood volume has been determined on both normal persons and cardiac patients with and without failure. A prerequisite for the determination of the circulating blood volume is that the dilution curves can be established and thereby the time when equilibrium appears can be determined.

In this work the results in each case are based on the mean values of a number of determinations. The mean value for the amount of the circulating blood corpuscles in normal cases was found to be 1,850 c.c., 1,998 grains, or 33.4 Gm. per kilogram of body weight.

The mean value of the compensated cases is in agreement with the normal values at 1,795 c.c., 1,939 grains, and 31.8 Gm. per kilogram of body weight. The total blood volume in the normal cases is 73.5 c.c. per kilogram of body weight; and in the compensated cases 71.8 cubic centimeters. Two cases of heart failure—and particularly one of them—show a considerable increase in both the amount of blood corpuscles and the circulating blood volume. The other case has been followed with repeated determinations after all signs of failure had disappeared. A great decrease in the circulating blood volume of no less than 28 per cent took place simultaneously with the appearance of the interesting phenomenon that the amount of red blood corpuscles also decreased by 18 per cent.

AUTHOR.

Wiggers, C. J.: The Failure of Transfusions in Irreversible Hemorrhagic Shock. *Am. J. Physiol.* 144: 91, 1945.

If reduction in circulating volume and in venous return, due either to exemia or to failure of a venopressor mechanism, are dominant factors in the circulatory failure which follows substantial infusions of adequate solutions, it may be anticipated that effective central venous pressures are reduced, as they are after large hemorrhages. It has been found that this is true in only eighteen out of forty-eight dogs submitted to our standardized technique for production of hemorrhagic shock.

The additional observations that effective venous pressures immediately after death from hemorrhagic shock are essentially within normal ranges and that the static circulatory equilibrium produced by prolonged vagal inhibition of the heart is also essentially normal fail to support the views that capillary transudation, pooling of blood in the vascular system, or failure of any venopressor mechanism represent the essential irreversibility factor in the majority of our animals.

The results strongly suggest that failure of transfusions in shock are not necessarily due to unsuitability of solutions used nor chiefly to loss of plasma or solutions through damaged capillaries or failure of a venopressor force, but, frequently at least, are attributable to myocardial depression, i.e., to a reduced reaction to equivalent venous filling pressures.

AUTHOR.

Bourne, G.: Ligature of Patent Ductus Arteriosus. *Brit. Heart J.* 7: 91, 1945.

In infected cases of patent ductus arteriosus, successful ligature of the ductus brings about a lasting cure.

In noninfected cases it may be most successful even at the stage when heart failure is developing.

AUTHOR.

East, T.: Ligation of the Patent Ductus Arteriosus. *Brit. Heart J.* 7: 95, 1945.

Ligation of the patent ductus arteriosus has been performed in thirteen cases. No anxiety arose in any case following operation. One patient, infected before operation, died later. One other patient died of septicemia which started after nine days' normal convalescence. It may possibly have arisen as a result of the operation, but there was no direct evidence of this.

The conclusion is that ligation is a good method of treatment in any patient with patent ductus arteriosus; the sooner after the sixth year, the better.

AUTHOR.

Moses, C.: The Effect of Digitalis, Epinephrine, and Surgery on the Response to Heparin. *J. Lab. & Clin. Med.* 30: 603, 1945.

A study of the response of individuals to the intravenous administration of 0.15 mg. of heparin per kilogram of body weight is presented.

No significant decrease in heparin tolerance was obtained after the administration of digitalis or epinephrine or after major surgery.

AUTHOR.

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TRAUMATIC RUPTURE OF THE NORMAL AORTA IN YOUNG ADULTS

REPORT OF TWO CASES

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TRAUMATIC rupture of the thoracic portion of the normal aorta in young adults is rare. The literature reveals many instances of rupture of different portions of the aorta in older age groups; the majority of these were associated with extrinsic erosions, inflammation, degeneration, and trauma, and a few occurred where there were structural abnormalities such as hypoplasia and coarctation. Two cases of complete rupture of the healthy thoracic aorta are reported in this paper; both occurred as a result of automobile accidents within two weeks of each other. We shall also discuss a few cases, reported in the literature, in which traumatic rupture of the normal aorta at the same site occurred in young adults. This age group, of course, includes the majority of the Armed Forces, and in this group the least degenerative changes are likely to have taken place.

Griffiths,¹ in 1931, described the case of a man, 26 years of age, who was dead when admitted to the hospital. According to his history he had been involved in a motorcycle accident. At necropsy a T-shaped rupture of the aorta just beyond the origin of the great vessels was found, which places the site of this rupture almost in the same area as in the two patients observed by us. Kleinsasser,² in 1943, reported the case of a man, 36 years of age, who, while walking, had been struck by a truck and thrown 30 feet. He was dead on admission to the hospital. At post-mortem examination the aorta was found to be incompletely severed at the junction of the aortic and thoracic portions. Some other interesting examples of traumatic rupture of the healthy aorta at the same and other sites in a little older age group are also reported here: Copeland's³ patient was a 40-year-old man with rupture of the descending aorta; Kuhn's⁴ patient was a 49-year-old man with "rupture of the lining of the aorta just as it springs from the left ventricle of the heart." This man did not die for ten days after the trauma which resulted in aneurysm and rupture. Kemp⁵ reported the case of a 46-year-old man with a transverse tear of the aorta just beyond the line of the aortic valve. Jaffe and Sternberg⁶ and Shennan⁷ found in aviators who had fallen from various heights, transverse aortic lacerations near the ligamentum arteriosum and the great arterial trunks.

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ANATOMY OF AORTA

Consideration of the anatomy of the aorta in this area shows that the descending aorta is divided into two portions, the thoracic and the abdominal, in topographical correspondence with the two great cavities of the trunk in which it is situated.⁸ The arch of the aorta ends at the left side of the lower border of the fourth thoracic vertebra, and the diameter in this portion is about 23 millimeters.⁹ The thoracic aorta is situated in the posterior mediastinal cavity. It begins at the lower border of the fourth thoracic vertebra, where it is continuous with the aortic arch, and ends in front of the lower border of the twelfth vertebral body at the aortic hiatus in the diaphragm.⁸

CASE REPORT

CASE 1.—A man, aged 32 years, was riding in a one-fourth ton "peep" which overturned. The vehicle rolled over once and then righted itself. The man was found dead, hanging from the vehicle with his feet caught under the dashboard, apparently having sustained the weight of the car on his body.

Autopsy.—External examination: The patient, a 32-year-old man, was well developed and well nourished; he had numerous linear abrasions over the anterior thorax and several contusions over each ilium. There was a marked depression on palpation in the region of the tenth thoracic vertebra with movement of the spinous process.

Internal examination: (1) Dorsal dissection: Incision was made over the spinous processes from the first cervical to the twelfth thoracic vertebrae, and the soft tissues were dissected away. There was a fracture of the spinous process of the tenth vertebra. (2) Ventral dissection: The body was opened by a Y incision. When the breast plate was removed, examination of the thorax revealed fractures of the third rib, right, anterior; the fifth rib, bilateral, anterior; and the eighth rib, right, posterior. There was no displacement of the fragments, but the intercostal muscles and the parietal pleura of the fifth and seventh intercostal spaces were lacerated. The heart was normal. The left thoracic cavity contained about 2,500 c.c. of blood and clots with the lung floating on the surface. The aorta appeared as a white tube cut cleanly at the junction of the arch and thoracic aorta lying within a mass of infiltrated, bloody, connective tissue. The rupture was at right angles to the length of the artery. The aorta appeared healthy, and the intima was smooth and devoid of dilatations and plaques. The lungs were normal; no fractures of the skull and no injury to the abdominal viscera was noted.

Microscopic Report.—Heart and great vessels: The myocardium showed no significant change. The aorta had areas of periadventitial hemorrhage. The aortic wall showed no significant abnormality.

The cause of death was rupture of the thoracic aorta with exsanguination.

CASE 2.—A man, aged 24 years, was riding in a light civilian automobile, which was traveling at a high rate of speed, and failed to make a curve on the road. The vehicle overturned several times; he was thrown through the left side of the windshield, hitting his head on the frame as he was catapulted from the car, and killed.

Autopsy.—External examination: Inspection revealed that the skull was laid open from the left orbit to the left occiput; the dura and the cortex of the brain were exposed, as the entire roof of the skull was broken off in one piece, resulting in multiple fractures of the bones of the left side of the face and skull. There were numerous abrasions on both sides of the chest at the nipple line and on both iliac crests.

Internal examination: The body was opened by a Y incision; examination of the thorax revealed fracture of the first, fourth, fifth, and sixth ribs at the right anterior portion of the chest; the first rib was the only one to pierce the right lung, causing a 2-cm. laceration at the very apex. The intercostal muscles and the parietal pleura were lacerated between the third, fourth, fifth, and sixth ribs on the left side. The left thorax contained about 600 c.c. of blood and several large blood clots. The heart was normal. The aorta was gaping with torn, jagged edges at the junction of the arch and the thoracic aorta. The rupture was caused by a transverse laceration completely severing the entire thickness of the vessel. The aorta was structurally normal, and there was no evidence of atheromatous degeneration. The lungs were healthy except for a small laceration in the right apex.

The liver presented multiple lacerations on both surfaces. No other abdominal viscera were injured.

Microscopic Report.—Heart and great vessels: There were no significant changes in the myocardium or aortic wall.

The cause of death was multiple skull fractures with maceration of the brain and rupture of the thoracic aorta.

DISCUSSION

The dynamics of rupture of the thoracic aorta of healthy young adults is of particular interest. A pressure of 1,000 mm. Hg was not sufficient to rupture the aorta of individuals between 20 and 40 years of age according to the studies of Klotz and Simpson,¹⁰ although Oppenheim¹¹ reported that a pressure of 3,000 mm. Hg was sufficient to rupture the normal human aorta. These figures are no doubt high, since rupture of the aorta in normal healthy individuals probably occurs only when sudden terrific force is applied to the thoracic cage. This violent force may no doubt be either direct or the result of contrecoup. In our two cases an element produced by torsion of the head and trunk doubtless was an important factor in bursting the aorta.

The site of rupture in our patients was distal to the emergence of the major branches of the aorta which is the relatively mobile point of the thoracic aorta. It becomes apparent that a sudden blow displacing the thoracic structures might cause a rupture in this mobile section either by direct or contrecoup force. In both our patients there was fracture of a few ribs but displacement of only one on the right side. The normal thorax is not a rigid structure and can be compressed in almost any diameter, although since resilience is high in this age group, such condition probably only added to the element of torsion to the thoracic contents. Wilson and Roome¹² feel that, if the blow is received at the beginning of diastole of the heart, the aorta is then completely distended with blood and rupture is more likely to occur. The opinion of Warfield¹³ is that the important factor in traumatic injuries of the heart and the aorta or its root occurs in full inspiration and that the sudden compression of the chest finds the heart caught and held between the inflated lungs which may result in rupture of the aorta. It is of interest that, in traumatic dissecting aneurysm, the site of predilection of intimal rupture is usually at or near the attachment of the obliterated ductus arteriosus (Botallo), just above the aortic valve and commonly on the posterior wall, near the aortic attachment of the ligamentum arteriosum, which acts as another point of fixation. These areas of fixation favor Rindfleisch's¹⁴ theory that fixation predisposes to injury and also Abbott's¹⁵ belief that, in these regions, the aorta may be congenitally weak.

In light of the absence of abnormalities on macroscopic and microscopic study of the aorta of our two cases, it is clear that complete transection of all the coats of the aorta owing to trauma in these two young adults is in marked contrast to spontaneous rupture of the aorta resulting from a process described by Erdheim¹⁶ as medionecrosis aortae idiopathica. The latter pathologic process may occur in young adults as shown by Taylor and Morehead.¹⁷ It is of particular interest that Schnitker and Bayer¹⁸ found in 580 recorded cases of dissecting aneurysm of the aorta that 24.31 per cent occurred in individuals under the age of 40 years. They felt that the lesion usually resulted from cystic necrosis of media.

We agree with the opinion of Collins and D'Alessio¹⁹ that the clinical syndrome produced by rupture of the aorta following trauma is caused by

surgical shock, but measures directed at combating shock and supporting the circulation are fruitless. Injuries of the intrapericardial portion of the aorta have been amenable to repair because of the surrounding structures, but perforating types of injury to the extrapericardial portion usually result in early death. Dshanelidze,²⁰ in 1922, reported the successful suturing of a wound of the thoracic aorta. Blalock,²¹ in 1932, successfully sutured an ice-pick wound of the intrapericardial portion of the ascending aorta in a Negro. Elkin's,²² in 1941, also reported the successful suture of a wound of the ascending aorta produced by an ice pick.

SUMMARY

1. Complete rupture of the normal thoracic aorta in young adults is rare.
2. Traumatic rupture at the junction of the arch and the thoracic portion probably occurs, because this is the most mobile portion of the aorta.
3. Rupture probably results from a sudden terrific blow to the thorax with both direct and contrecoup forces plus sudden torsion of the head and trunk.
4. Two cases of traumatic rupture of the normal aorta involving the junction of the arch and the thoracic portion are reported.

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STUDIES CONCERNING THE ETIOLOGY AND PATHOGENESIS OF NEUROCIRCULATORY ASTHENIA

II. THE MECHANISMS* UNDERLYING THE GIDDINESS FOUND IN PATIENTS WITH NEUROCIRCULATORY ASTHENIA

MAJOR MEYER FRIEDMAN, M.C.†

INTRODUCTION

GIDDINESS was early recognized^{1, 2, 3} as an occasional manifestation of neurocirculatory asthenia (NCA), and scarcely any comprehensive review devoted to this syndrome fails to mention the occurrence of this symptom. But if this phenomenon has been recognized universally, it has not been investigated satisfactorily in regard to the mechanism responsible for its production. Soley and Shock⁴ described giddiness occurring in their patients after the induction of hyperventilation, and they implied that the alkalosis therein produced might have given rise to it. But sufficient evidence has been accumulated^{5, 6, 7} to make it evident that, although hyperventilation may occasionally be found in NCA patients, it is not an initial etiological factor of any real importance in the production of the syndrome from which they suffer. MacLean and his associates^{8, 9} have studied NCA patients and have suggested that the giddiness from which they suffer at diverse times might be due to a defect in the return of venous blood to the heart. Since no determinations of venous pressure apparently were taken during their experiments, no real evaluation of their findings is possible.

In the present communication, the results are given of studies made concerning the incidence and the pathogenesis of giddiness in a group of forty-one young soldiers (average age: 26 years) suffering from neurocirculatory asthenia. They indicate that this symptom results from physiologic dysfunction of the cardiovascular system of these patients. It was found, too, that this phenomenon could be reproduced experimentally in susceptible individuals if a particular type of physiologic dysfunction were produced in them.

EXPERIMENTAL OBSERVATIONS

In the group of forty-one patients studied, twenty-nine, or approximately 70 per cent of them, gave a history of experiencing frequently an unpleasant sensation, best described by the term giddiness. Questioning revealed that, although this sensation was experienced by some individuals under varied conditions, the majority of patients experienced their giddiness intermittently and only at those times during which they abruptly changed from the supine to the erect position.

In five of our patients however, giddiness invariably occurred each time they arose from the sitting or supine position. In three of these five patients, this constantly occurring sensation had become so severe that they took particular care to rise quite slowly from the supine or sitting position.

It was found that all giddy NCA patients differed clinically from patients with orthostatic hypotension in several important respects. For instance, the

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former type of patient never exhibited any localized or generalized deficiency in perspiration or hypotension, and the giddiness experienced was always transient, occurring immediately after arising and disappearing in five to ten seconds. Furthermore when giddiness was complained of by an NCA patient, it was observed that he also was suffering severely from other recognized symptoms and signs of the syndrome.

Preliminary studies were made on three of the five patients who, as related, invariably experienced giddiness on arising. These studies consisted of measuring their blood pressure, venous pressure, and pulse rate and observing the occurrence of giddiness before and during their assumption of the erect position after the supine position had been maintained for fifteen minutes. For purposes of control, the same four observations were made on NCA patients without giddiness and on four young normal individuals. The venous pressure was determined by means of a direct puncture of the right antecubital vein with an intravenous needle (18 caliber) attached by rubber tubing (30 cm. in length and 2 mm. in diameter) to a glass manometer (1 mm. in diameter). The entire apparatus was filled with 3.5 per cent sodium citrate solution. It was found that a stable determination could be obtained within ten seconds.

It was found (Table I) that, although the venous pressure fell about equally in the three groups on arising, giddiness was experienced only by the susceptible NCA patients. Quite significantly, too, it was observed (Table I) that, whereas the pulse pressure diminished but 33 per cent in NCA patients without giddiness and 17 per cent in normal individuals, it had diminished 78 per cent in the giddy, NCA patients. The pulse rate also had increased disproportionately in the giddy patients as compared with the changes in pulse rate of the other two groups.

The two remaining patients who invariably experienced giddiness on arising were examined fluoroscopically before and during their assumption of the erect from the supine position. Two NCA patients without giddiness and two normal individuals were likewise observed. It was noted (Table II, B and C) that the subjects not susceptible to giddiness on arising showed little change on fluoros-

TABLE I. THE HEMODYNAMIC EFFECTS OF ABRUPT CHANGE OF POSITION IN THE GIDDY NCA PATIENT, IN THE NCA PATIENT WITHOUT GIDDINESS AND IN THE NORMAL INDIVIDUAL

CASE	SUPINE POSITION			ERECT POSITION		
	BLOOD PRESSURE*	VENOUS PRESSURE†	GIDDINESS	BLOOD PRESSURE‡	VENOUS PRESSURE§	GIDDINESS
<i>A. Giddy NCA Patients</i>						
AB	135/85	5.0	None	125/110	3.0	Severe
ADBC	115/80	---	None	110/105	---	Severe
ABCDE	120/70	8.0	None	105/95	0.0	Severe
Average:	123/78	6.5		113/103	1.5	
<i>B. NCA Patients Without Giddiness</i>						
CDBA	125/70	10.5	None	115/85	5.0	None
BDAC	135/95	4.5	None	145/95	0.0	None
ADCB	120/75	9.0	None	110/90	6.0	None
ACBDE	115/75	---	None	115/95	---	None
Average:	124/79	8.0		121/91	3.6	
<i>C. Normal Individuals</i>						
A-10	125/75	8.0	None	115/70	-1.0	None
A-11	120/70	8.0	None	115/80	6.0	None
A-12	110/80	---	None	120/84	---	None
A-13	135/80	---	None	130/82	---	None
Average:	122/76	8.0		120/82	2.5	

*Blood pressure in mm. of Hg obtained after patient was in supine position for fifteen minutes.

†Venous pressure in cm. of H₂O as obtained by direct puncture of the right antecubital vein.

‡Blood pressure taken immediately upon assumption of the erect position.

§Venous pressure taken immediately upon assumption of the erect position.

copy other than a slight increase in rate of cardiac contraction, but the two giddy NCA patients (Table II, A) not only showed a marked increase in rate of cardiac contraction but also a sudden, abrupt decrease in the width and in the pulsatile excursion of the pulmonary artery (conus) which lasted for several seconds. The pulmonary artery then widened and was observed to pulsate again; the heart slowed and contracted more vigorously. The two patients complained of their giddiness a few seconds after the pulmonary artery was seen to narrow; their giddiness was no longer felt after the pulmonary artery was observed to widen and pulsate normally again.

These findings of a marked decrease in pulse pressure together with fluoroscopic evidence of marked diminution in the width of the pulmonary artery and in its degree of pulsation in those NCA patients experiencing giddiness on arising suggested that not only were abnormal hemodynamics observed to be present before the onset of giddiness but also that these same hemodynamic abnormalities might have led to cerebral changes which in turn gave rise to the sensation experienced by these patients. However, besides the hemodynamic abnormalities occurring after abrupt change of position, the possibility existed that the vestibular apparatus also might have been reflexly stimulated in these giddy patients and that some activity set up in this organ by such stimulation might have induced the giddiness. The last possibility later was eliminated, for it was found that giddiness could not be produced in susceptible patients either by flexing and extending the head upon the trunk in the erect or supine position or by making the patient quickly assume the supine position after prolonged standing. In short, the primary mechanism responsible for the abnormal sensation experienced by the giddy NCA patient appeared to be connected with some hemodynamic dysfunction. What was still undetermined was whether there was an *abnormally* decreased return of venous blood to the heart when the patient arose (as is supposed to occur in the patient with orthostatic hypo-

TABLE II. THE FLUOROSCOPIC EXAMINATION OF THE GIDDY NCA PATIENT, OF THE NCA PATIENT WITHOUT GIDDINESS AND OF THE NORMAL INDIVIDUAL, DURING CHANGE OF POSITION AND DURING THE PERFORMANCE OF THE FLACK TEST

ASSUMPTION OF THE ERECT FROM THE SUPINE POSITION					PERFORMANCE OF THE FLACK TEST*			
CASE	MEDIAS-TINAL COMPRES-SION?	INCREASE IN HEART RATE?	DIMINU-TION IN WIDTH OF PUL-MONARY ARTERY?	VISIBLE PULSATION IN PUL-MONARY ARTERY?	MEDIAS-TINAL COMPRES-SION?	INCREASE IN HEART RATE?	DIMINU-TION IN WIDTH OF PUL-MONARY ARTERY?	VISIBLE PULSATION IN PUL-MONARY ARTERY?
<i>A. Giddy NCA Patients</i>								
BA	None	Marked	Marked	Very little	Marked	Marked	Marked	None
AB	None	Marked	Marked	Very little	Marked	Marked	Marked	None
DBCA	-----	-----	-----	-----	Marked	Marked	Marked	None
ABC	-----	-----	-----	-----	Marked	Marked	Marked	None
CABD	-----	-----	-----	-----	Slight	Marked	Marked	None
ABCD	-----	-----	-----	-----	Slight	Marked	Marked	None
BACD	-----	-----	-----	-----	None	Marked	Marked	None
ACBD	-----	-----	-----	-----	Slight	Marked	Marked	None
<i>B. NCA Patients Without Giddiness</i>								
ABDC	None	Slight	None	Unchanged	None	Moderate	None	Unchanged
BDCA	None	Slight	None	Unchanged	Slight	None	None	Unchanged
BDAC	-----	-----	-----	-----	Slight	Slight	None	Unchanged
CDBA	-----	-----	-----	-----	Slight	Slight	None	Unchanged
<i>C. Normal Individuals</i>								
R-8	None	Slight	None	Unchanged	Marked	Slight	None	Unchanged
R-7	None	Slight	None	Unchanged	Slight	Slight	None	Unchanged
R-6	-----	-----	-----	-----	None	Slight	None	Unchanged
R-5	-----	-----	-----	-----	Slight	Slight	None	Unchanged
R-4	-----	-----	-----	-----	None	None	None	Unchanged

*Observations made from beginning of Flack test up to twenty seconds of continuous blowing.

tension⁸), or whether there was an abnormal response of the cardiovascular system of the susceptible patient to the *normally* decreased return of venous blood to the heart which occurs on assumption of the erect from the supine position.

If the giddiness of the patients under observation arose from the hemodynamic effects originally initiated by decreased return of venous blood to the heart, such giddiness should be induced by any measure compressing the veins leading into the right auricle, thus inhibiting the venous return. To accomplish this reduction in venous return, a modification of the Flack test¹⁰ was used in which the patient sustained a mercury column at a level of 30 mm. Hg for twenty seconds by blowing into a rubber tube connected to the bottom of the receptacle containing the mercury. A reduction in venous return to the heart was accomplished supposedly by the resulting increase in intrathoracic pressure.⁸ The advantage of this test was that it entailed no change in position, thus eliminating possible influences upon the vestibular system and that it also allowed sufficient time for various hemodynamic measurements not able to be obtained in the previously described experiments.

Nineteen patients with neurocirculatory asthenia (twelve of whom gave a history of very frequent giddiness on arising) and eight normal individuals were tested in the erect position. Six of the twelve giddy patients were tested also in the supine position. The presence or absence of giddiness, the blood pressure, the venous pressure, and the pulse rate were determined before and during the performance of the Flack test. In some subjects, determination of the arm-to-tongue circulation time (calcium gluconate method) before and during the test also was obtained.

Table III, A reveals that each of the twelve NCA patients who gave a history of experiencing giddiness complained of the same sensation during the Flack test, and declared that it was identical with that which they usually had experienced on arising quickly. The control subjects, however (Table III, C and D), with the exception of two individuals (A-3 and A-8) experienced no subjective results other than a feeling of fullness in the head and neck during the test.

More important than the subjective sensations felt by these patients was the striking and differential reaction of their blood pressures during the test. For, although most NCA patients without giddiness and normal individuals showed either no change or a slight rise in their systolic pressures after twenty seconds of blowing (Table III, C and D), a very slight decrease in systolic pressure occurred in nine of the giddy NCA patients (Table III, A). More significant was the striking rise of the diastolic pressure in the giddy patient (average rise: 30 mm. Hg) during the test as compared to the rise in the NCA patients without giddiness (average rise: 14 mm. Hg) and that in the normal individuals (average rise: 17 mm. Hg). This marked increase in the diastolic pressure of the giddy patients during blowing resulted in an average pulse pressure of 8 mm. Hg (Table III, A) and explained the disappearance of the radial pulse observed and commented upon by Master.¹¹ The great enhancement and the slight diminution noted in diastolic and systolic pressures, respectively, of the giddy NCA patients during the Flack test must be taken as evidence that a marked peripheral arteriolar constriction must have occurred to have caused these pressure changes. It should be noted, finally, that these blood pressure changes occurring in the giddy NCA patient during the Flack test were similar to those observed when the same type of patient changed his position (compare Tables I, A, and III, A).

TABLE III. THE HEMODYNAMIC EFFECTS OF THE FLACK TEST IN THE GIDDY NCA PATIENT (IN ERECT AND SUPINE POSITION), IN THE NCA PATIENT WITHOUT GIDDINESS AND IN THE NORMAL INDIVIDUAL

CASE	BEFORE FLACK TEST					DURING FLACK TEST*				
	GIDDI- NESS	B.P.†	V.P.‡	PULSE§	CIRC. TIME	GIDDI- NESS	B.P.	V.P.	PULSE	CIRC. TIME
<i>A. Giddy NCA Patients in Erect Position</i>										
AB	None	145/90	9.0	88	13	Very severe	125/118	30.5	130	Over 30
BA	None	130/88	3.5	84	--	Very severe	125/122	25.0	144	----
ABC	None	110/70	8.0	86	--	Very severe	105/103	32.0	120	----
BAC	None	135/90	4.0	82	12	Very severe	160/150	28.0	132	Over 30
ABCD	None	125/85	5.0	90	11	Very severe	115/108	32.0	144	20
ACBD	None	110/70	6.5	84	--	Very severe	105/100	27.0	102	----
CABD	None	120/80	---	110	--	Very severe	122/118	---	132	----
BCDA	None	120/80	10.0	84	--	Very severe	118/110	31.0	100	----
ADBC	None	120/76	2.0	80	--	Very severe	112/105	24.0	120	----
ABCDE	None	130/85	---	90	--	Moderate	125/110	---	125	----
ACBDE	None	120/95	---	80	--	Moderate	125/110	---	122	----
ABCED	None	135/95	---	84	--	Very severe	125/118	---	120	----
Average:		125/84	6.0	87			122/114	28.6	124	
<i>B. Giddy NCA Patients in Supine Position</i>										
AB	None	140/80	10.5	80	--	Very severe	120/118	36.5	120	----
BA	None	125/80	8.0	80	--	Very severe	120/116	33.0	132	----
BAC	None	135/85	10.0	84	--	Very severe	150/145	34.0	128	----
ACBD	None	110/70	9.0	80	--	Very severe	105/95	32.0	110	----
ABCED	None	125/80	---	82	--	Very severe	138/132	---	118	----
ACBDE	None	125/80	---	76	--	Severe	125/115	---	116	----
Average:		128/81	9.3	80			126/120	33.9	120	
<i>C. NCA Patients Without Giddiness in Erect Position</i>										
ABDC	None	135/70	8.0	80	11	None	135/90	24.0	90	12
CDBA	None	130/80	8.0	80	--	None	140/90	22.0	85	----
BDCA	None	155/85	10.0	84	12	None	155/100	10.0	96	----
BDAC	None	145/95	2.0	96	--	None	155/105	21.0	132	----
ADCB	None	135/75	9.0	88	--	None	135/90	9.0	96	----
ACBED	None	115/75	2.5	72	--	None	115/95	10.0	132	----
R-1	None	125/80	5.5	---	--	None	125/90	8.0	---	----
Average:		134/80	6.4	83			137/94	14.8	105	
<i>D. Normal Individuals in Erect Position</i>										
A-1	None	130/80	6.5	84	12	None	125/90	10.5	92	13
A-2	None	135/90	8.0	80	10	None	133/102	10.0	108	12
A-3	None	125/70	6.0	70	--	None	135/100	32.0	90	----
A-4	None	115/80	6.0	80	--	None	125/90	16.0	88	----
A-7	None	105/80	4.5	88	--	None	130/105	15.5	96	----
A-8	None	115/85	7.0	84	--	None	130/105	29.0	94	----
A-9	None	120/90	2.0	76	--	None	120/105	18.0	90	----
A-10	None	115/65	---	---	--	None	120/80	---	---	----
Average:		120/80	5.7	80			127/97	18.7	94	

*All observations taken after twenty seconds of blowing.

†Blood pressure in millimeters of mercury.

‡Venous pressure (directly observed from right antecubital vein) in centimeters of water.

§Pulse rate per minute.

||Circulation time (calcium gluconate method) from arm to tongue.

In preliminary experiments, during which the blood pressure measurements were made before and five, ten, fifteen, and twenty seconds after the beginning of the Flack test, it was found that the patients never experienced giddiness until their pulse pressures decreased below 20 mm. of mercury. It was found, in addition, that the intensity or severity of their giddiness was directly proportional to the decrease in pulse pressure. These observations suggested that peripheral arteriolar constriction preceded the giddiness and possibly played a part in the production of the sensation felt by these patients.

The venous pressure was obtained as previously described in the three groups of subjects. After the control level had been established (within ten seconds), the subjects began the Flack test with the pressure manometer still connected to their veins. It was observed that in all three groups, the venous

pressure began to rise after five seconds of blowing. After approximately fifteen seconds of blowing, however, the venous pressure of the normal subject and the NCA patient without giddiness ceased to rise and became relatively stable. However, the venous pressure of the giddy NCA patient was observed to continue to rise as long as the patient continued to blow against the mercury column, even if, as in some cases, the test continued for thirty seconds. The measurements of the venous pressure shown in Table III, *A*, *C*, and *D* (recorded after twenty seconds of blowing) indicate that the average venous pressure of the giddy NCA patient (28.6 cm. H₂O) was approximately twice as high as that of the NCA patient without giddiness (14.8 cm. H₂O) and considerably higher than that of the normal individual (18.7 cm. H₂O). It will be noted that in two of the normal subjects (Table III, *D*, A-3 and A-8), the venous pressure was high at the end of twenty seconds. Both of these individuals also were found to experience giddiness at this time. Since many an otherwise normal young adult will give a history of having experienced giddiness on arising, it is not surprising that considerable variation was found in the objective and subjective results of our control group of subjects, in relation to the venous pressure and sensation of giddiness. This rather suggests that the NCA patient with giddiness differs quantitatively, not qualitatively, from the average individual. However, the far greater average rise in venous pressure in the giddy NCA patient during the Flack test indicates that, in them, the venous flow was either abnormally increased during blowing or that the test produced a greater obstruction to venous flow in the mediastinum of the giddy NCA patient. In view of the fact that arteriolar constriction was present, it was assumed that there was a greater venous flow because of the consequent greater expulsion of blood from the arteriolar system, for no satisfactory reason could be found for assuming that the Flack test produced a greater mechanical obstruction in the mediastinum of the giddy NCA patient than it did in the mediastinum of the other types of subjects. It must be added, too, that perhaps there was constriction of the venules and capillaries in the giddy NCA patients during the test which would increase the venous flow also. However, no proof of this last assumption was able to be obtained.

When giddy NCA patients were compared with NCA patients without giddiness and with normal individuals under the fluoroscope before and during the performance of the Flack test, it was found that not only did the heart rate of the giddy patient increase abnormally as compared with the heart rate of the controls but also the pulmonary artery of the giddy patient was seen to narrow markedly and pulsatile excursions of the same artery could not be detected. In other words, the fluoroscopic observations of the giddy patient during blowing, like the blood pressure changes, were similar to those following change of position (Table II, *A*). About five seconds after the pulmonary artery was seen to narrow and apparently cease to pulsate, the patients complained of giddiness. When they ceased blowing, the pulmonary artery was seen to resume its normal size and action. After a few seconds, the patients stated that they were no longer giddy.

In connection with the fluoroscopic examinations, the determinations of the arm-to-tongue circulation time produced important results. For, whereas in two of the three giddy patients so tested (Table III, *A*) the arm-to-tongue time was less than thirteen seconds before blowing, no sensation could be perceived if the calcium gluconate were injected into the antecubital vein five seconds after blowing had begun even though the latter were continued for thirty seconds. This observation, when considered with the abrupt changes seen in the pul-

monary artery during blowing, indicated quite conclusively that during the test very little or no forward flow of blood occurred in these giddy patients; otherwise they would have felt the injected calcium either in their tongues or elsewhere in their bodies. When these same two patients ceased blowing, they felt the previously injected calcium in their tongues approximately six seconds after cessation of blowing. This last observation suggested that the blood containing the calcium had been impeded somewhere in the pulmonary circuit; otherwise the calcium would not have been felt in the tongue so rapidly after blowing had been stopped.

DISCUSSION AND SUMMARY

Since both the Flack test and abrupt change of body position presumably decreased the return of venous blood to the heart, temporarily at least, in all individuals, it was not surprising to observe that the objective and subjective results noted in the giddy NCA patients during the Flack test were similar to those following abrupt change of position. The intense pulmonic and systemic vasoconstriction observed in the giddy NCA patient in each type of test was not a reaction to an abnormally lessened venous return to the heart because it was found that the giddy patient during the Flack test showed a higher venous pressure in the antecubital vein than the normal individual, indicating that the venous return from the upper extremity at least was above normal. Furthermore, there was no abnormal decrease in venous flow from the lower extremities in these giddy patients for the hemodynamic and subjective reactions of six such patients (compare *A* and *B* of Table III) during the Flack test were qualitatively and quantitatively identical whether they performed the test in the erect or supine position. This would not have been the case if there were an abnormally lessened venous flow from the lower extremities in the erect position. For this reason it seems impossible to escape the conclusion that the temporary and intense pulmonic and systemic vasoconstriction observed during the Flack test was due to a fundamental hyperirritability of the cardiovascular system of these patients to slight changes in the flow or pressure of venous blood returning to the right auricle—changes which in the normal individual evoke only slight and physiologically commensurate readjustments in the cardiovascular system.

In a previous article,¹² the hyperthermia present in many NCA patients was described. It was deduced from these same studies that the hypothalamus was affected in some manner in these hyperthermic NCA patients. In the present studies, the profound and generalized vasoconstriction which occurred in the giddy NCA patient following maneuvers which caused no comparable effect in the normal individual suggests that the portion of the autonomic nervous system concerned with this vasoconstriction, namely, the sympathetic nervous system, was hyperirritable or deranged in the giddy NCA patient. Since the main coordinating center of this portion of the autonomic nervous system lies within the hypothalamus,¹³ it is conceivable that this area of the brain may be involved in the pathogenesis of the giddiness found in the NCA patient. No direct proof, however, has been found to support this last conception.

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FURTHER EVIDENCE FOR THE PURELY VALVULAR ORIGIN OF THE FIRST AND THIRD HEART SOUNDS

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ALTHOUGH the fact that the first heart sound is of purely valvular origin is stressed in recent texts on physiology and on heart disease,¹ and has been borne out by many precisely recorded observations made recently, not all of the evidence in recent contributions has been emphasized in connection with this problem. On the other hand, evidence based on thoroughly unsatisfactory sound tracings has been interpreted as proving that there is an appreciable muscular element in the first and third sounds.^{2, 3} For a correct understanding of physical signs, the matter is of sufficient importance to be discussed more fully. Most close students of heart sounds can agree with the discussion of the first sound presented by White and his colleagues,¹ based on their own work and on that of others. These careful students have found no evidence of audible vibrations due to the ventricular wall itself.

Smith^{2, 3} and his co-workers present tracings of the movements of the ventricular surface of the dog's heart, some of which show, superimposed on the cardiogram, oscillations of low amplitude which undoubtedly are due to audible vibrations arising in the heart. These records all were obtained from the normally functioning heart. In these papers they present tracings obtained from the heart after cutting off venous inflow, filling the ventricular chambers with balloons, ligating around the A-V sulcus,² or immobilizing the valves with special devices introduced through the auricles.³ None of these tracings show any vibrations of audible frequency, except possibly one with a balloon in the ventricles. As rubbing such balloons with a wet object is a standard trick in sound production, known to most children, this latter observation is not surprising and is irrelevant to a study of the heart sounds.

Movements of the heart wall, which for the most part appear as single swings away from the base line, with durations of 0.08 to 0.28 second, are marked as

"sounds," and on the basis of this unwarranted identification it is concluded that significant elements of the first and third sounds originate in the ventricular wall itself.

Since 16 cycles, or double vibrations, per second is given as the lower limit of human hearing in audiometer tests, and since 12 cycles per second is accepted by physiologists as the lowest pitched sound ever audible to man, any such cardiac movements, with cycles of 6 to 1.8 per second, obviously are inaudible. It may be true that the authors heard "dull" sounds when they listened to binaural stethoscopes attached to their recording system as these records were being inscribed, but this merely proves that puffs of air, in a closed system, can set the eardrums in vibration.

Wiggers and his co-workers^{4, 5} have carefully studied the recording of heart sounds, and have shown what acceptable records look like. They have recognized the artifacts produced by applying funnels or diaphragms directly to the heart, and by not having an open system to obviate mechanical pressure waves. All these precautions were ignored by Smith and his co-workers, and few of their records show adequate records of sounds, while movements of the heart lasting through half of the cardiac cycle are recorded as tall broad waves of far greater amplitude than any of the oscillations of audible frequency. Waves whose full cycle duration would be 0.16 to 0.56 second cannot be regarded as sounds, for which the shortest cycle length is, at most, 0.08 second.

Boyer⁶ had already proved that the third heart sound originated in the heart and not, as had been suggested, from the heart's striking the chest wall. He showed that an oscillation of very low amplitude and frequency could be caused by the heart striking the diaphragm of the recording pickup, but this in no way resembled the third sound recorded from a cardiometer within which the heart was suspended so that it could not touch the walls (Figs. 2, *B* and 2, *C*⁶).

Lewis and Dock⁷ had recorded silent ectopic beats which occurred 0.02 second after the second sound, and beats of similar electrocardiographic contour occurring 0.10 second after the second sound but associated with very loud first sounds. This proved that in man the first sound does not occur during a systole which precedes the opening of the atrioventricular valves. They had shown that third heart sounds which varied during respiration were associated with variable degrees of sudden diastolic retraction of the apex and presumably of reflux toward the auricle. Since the first and third sounds are indistinguishable in quality, and either may exceed the other in intensity, they concluded that the first and third sounds originated in sudden tensing of the atrioventricular valves, by systole or by reflux.

MacLeod and Cohn,⁸ using a piezoelectric pickup and recording from the interior of the auricles and ventricles, showed that sound vibrations are recorded only very close to the semilunar cusps (second sound most intense) and in the atrioventricular opening (first sound only). Their system, designed to record pressure changes, is relatively insensitive to sound, and shows how rapidly the sounds fade as the pickup moves into either auricle or ventricle from the valve area. Thus, for the first time, the points of origin of the first and second sounds have been sharply and surely defined (Fig. 3, *VI* and *X*⁸).

Dock⁹ had already shown, using the recording system described by Wiggers, that the first sound of the dog's heart disappeared when the venous inflow was arrested or the atrioventricular valves were immobilized by ligatures. While Smith's records are unsatisfactory technically, they confirm these observations since the vibrations of audible frequency in early systole of the normally beating

heart, apparent in Fig. 2 *A*,³ disappear at once on closing off the venous inflow (Fig. 2 *B*³). In Fig. 2 *B* et seq. only the cardiogram, with oscillations of far less than audible frequency, remains. Thus Smith's experiments actually confirm those done with appropriate methods of recording heart sounds.

It cannot be too strongly urged that those who study heart sounds filter out the mechanical oscillations as far as possible, and that only double vibrations lasting 0.06 second or less be regarded as sounds. Experience has shown that gallop phenomena can be recorded when they are inaudible, so that in clinical study records of the vibrations of small intensity or subaudible pitch may be of real value.

It is extremely doubtful whether the ear ever detects the vibrations arising in the auricles and great vessels just before and after the main vibrations of the first sound.¹ It is certain that variations in intensity and quality of the apical first sound are closely related and probably due to variations in the intensity and synchronization of the vibrations which arise in early systole from sudden tensing of the right and left atrioventricular valves. Clinically then, the first sound is purely valvular.

CONCLUSIONS

By recording sounds from the interior of the dog's heart, MacLeod and Cohn sharply localized the atrioventricular valves as the site of origin of the first sound and the semilunar valves as the site of origin of the second. Rapid vibrations also were recorded near the semilunar valves very early in systole.

The site of origin of the third heart sound has not been determined with precision, but as the sound occurs in normal dogs given rapid saline infusions, the technique of MacLeod and Cohn can easily be applied by those who doubt the evidence, from observations on man, that this sound also arises in the atrioventricular valves. No experimental or clinical proof that any element of any of the normal sounds has its origin in the ventricular wall has yet been presented.

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THE INTRAVENOUS ADMINISTRATION OF LANATOSIDE C TO PATIENTS TAKING MAINTENANCE DOSES OF FOLIA DIGITALIS UP TO THE DATE OF HOSPITALIZATION WITH RECURRENT CONGESTIVE HEART FAILURE

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INTRODUCTION

IT HAS been suggested by Gold and DeGraff¹ that patients with auricular fibrillation need larger maintenance doses of digitalis when they are on the verge of, or in, congestive heart failure. Fahr and LaDue² demonstrated the need for higher maintenance doses of lanatoside C during the period of failure in patients with auricular fibrillation. Eight patients required an oral dose of 2.5 mg. to keep the heart rate below 80 while signs of heart failure were present, but 1 mg. to 0.5 mg. sufficed when these patients had established compensation. As yet, we have no adequate means of determining whether the patient with heart disease associated with regular sinus rhythm is receiving maximal therapeutic doses of digitalis. It seemed worth-while to us, therefore, to determine the therapeutic and toxic effect of the intravenous administration of lanatoside C (Cedilanid) to patients who developed congestive heart failure while taking maintenance doses of 0.1 to 0.3 Gm. of folia digitalis.

Many authorities strongly advise against the intravenous administration of cardiac glycosides to any patient who has taken digitalis within the preceding ten days,³ since uncontrollable nausea and vomiting, extrasystoles, pulsus bigeminus, ventricular tachycardia, ventricular fibrillation, heart block, or cardiac standstill may result.

However, during the course of a previous study,² intravenous injections of lanatoside C were given without toxic manifestations to several patients who erroneously denied previous digitalis dosage. Hence, we decided that this problem was worthy of further study.

METHOD

Thirty-one patients with congestive heart failure were given 0.8 mg. (half the digitalizing dose²) of lanatoside C intravenously, despite the fact that they had been taking 0.1 to 0.3 Gm. of folia digitalis daily for periods of weeks or months before the current admission. Twenty-two patients were given 1.2 mg. of lanatoside C intravenously, and nine patients received 1.6 milligrams. Of these sixty-two patients, thirteen had auricular fibrillation with apical pulse rates from 90 to 140, and forty-nine had congestive heart failure associated with regular sinus rhythm. All had venous pressures greater than 15 cm. of water on admission, and most of them had heart failure of high degree.

Fifty-one of the patients were between the ages of 41 and 80 years; thirty-seven were colored, and twenty-five were white. Forty-one had hypertensive heart disease; eleven had arteriosclerotic heart disease; eight had syphilitic heart disease; and two had rheumatic heart disease.

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Daily measurements were made of the venous pressure, vital capacity, and circulation time; the degree of pulmonary and peripheral congestion; the degree of dyspnea, orthopnea, and cyanosis; together with clinical notes concerning the heart rate, rhythm, and size, as well as the subjective state of the patient. No diuretics or other drugs were given except sedatives as needed for rest or relief of cough or pain. Fluid and salt intake was not restricted. Electrocardiograms were made on admission and the day after the intravenous administration of lanatoside C when possible. Maintenance doses of from 0.1 to 0.3 Gm. of folia digitalis were started six to twelve hours after the injection of the cardiac glycoside.

RESULTS

Table I summarizes the data obtained from all sixty-two patients. Thirty-six of the forty-nine patients with heart failure associated with regular sinus rhythm responded to the medication with a prompt stabilization of the venous pressure within two to six days. By stabilization we mean that the venous pressure fell significantly, reaching 10 cm. of water or lower, and the circulation time fell to a constant level, usually 16 to 28 seconds. In every instance, the previously elevated venous pressure and circulation time fell to levels approaching normal.

TABLE I*

NUMBER OF PATIENTS WITH				DOSAGE OF LANATO- SIDE-C	DAYS FOR STABILIZATION OF CERTAIN CRITERIA OF CONGESTIVE HEART FAILURE			NUMBER OF PATIENTS		
AURICU- LAR FIBRIL- LATION	REGU- LAR SINUS RHYTHM	ECG EVIDENCE OF DIGITALIS		(MG.)	CIRCU- LATION TIME	VENOUS PRES- SURE	DYS- NEA AND ORTHOP- NEA	SHOW- ING NO IM- PROVE- MENT	WITH TOX- ICITY	FATAL- ITIES
		BEFORE	AFTER							
6	25	9	10	0.8	6.6	2.0	5	3	0	5
6	16	12	7	1.2	5.8	6.8	4	2	1	4
1	8	3	3	1.6	5.0	6.0	4	0	0	2

*This is a summary of the data obtained from all sixty-two patients studied. See text.

TABLE II*

PA- TIENTS WITH AURICU- LAR FIBRIL- LATION	DOSAGE OF LANATO- SIDE C (MG.)	VENTRICULAR RATES				DAYS FOR STABILIZATION OF CERTAIN CRITERIA OF CONGESTIVE HEART FAILURE			NUMBER OF PATIENTS		
		120- 140	100- 120	90- 100	60	CIRCU- LATION TIME	VENOUS PRES- SURE	DYS- PNEA AND ORTHOP- NEA	SHOW- ING NO RE- SPONSE	WITH TOX- ICITY	FATAL- ITIES
6	0.8	1	2	2	1	6.5	7.0	6	2	0	0
6	1.2	3	3			5.0	5.6	4	0	0	1
1	1.6		1			5.0	5.0	4	0	0	0

*This is a summary of the data obtained from thirteen patients with auricular fibrillation. See text.

TABLE III*

PATIENTS WITH REGULAR SINUS RHYTHM	DOSAGE OF LANATO- SIDE C (MG.)	DAYS FOR STABILIZATION OF CERTAIN CRITERIA OF CONGESTIVE HEART FAILURE			NUMBER OF PATIENTS		
		CIRCU- LATION TIME	VENOUS PRESSURE	DYS-PNEA AND ORTHOP- NEA	SHOWING NO RESPONSE	WITH TOXICITY	FATAL- ITIES
25	0.8	5.8	7.1	4.4	1	0	5
16	1.2	5.5	5.8	4.2	2	1	3
8	1.6	8.7	8.0	6.0	0	0	2

*This is a summary of the data obtained from forty-nine patients with regular sinus rhythm. See text.

Tables II and III present the same data separately for patients with auricular fibrillation and for patients with regular sinus rhythm. Most of the discussion in the text, except as noted, refers to Table I.

If we compare the rapidity of response in these patients (all had initial venous pressures above 15 cm. of water) with that of a previously studied group of patients with regular sinus rhythm (Table IV), it will be seen that the venous pressures of the thirty-six patients now under discussion fell much more rapidly than did those of a "control group" of patients with comparable degrees of heart failure who were given no digitalis. This control group was a series of twenty-four patients who received no cardiac glycoside during their hospitalization. We feel, therefore, that the response of these thirty-six patients could not be attributed to bed rest alone.

TABLE IV. NORNAL SINUS RHYTHM*

THERAPY	TOTAL NO. OF CASES	AV. NO. OF DAYS FOR VENOUS PRESSURE TO FALL TO 8 CM. WATER	AV. NO. OF DAYS FOR ONSET OF DIURESIS	AV. NO. OF DAYS FOR SIGNIFICANT RISE —30%— IN VITAL CAPACITY	AV. NO. OF DAYS IN BED	AV. NO. OF DAYS IN HOSPITAL	MORTALITY %
<i>Venous Pressure > 15 Cm. of Water</i>							
Control	24	14.8 (14)	6.4 (12)	13.0 (11)	24.1 (12)	27.4 (13)	41.7
Lanatoside C	54	4.5 (39)	3.3 (31)	8.5 (32)	12.2 (33)	19.5 (27)	25.9
<i>Venous Pressure < 15 Cm. of Water</i>							
Control	18	3.7 (12)	3.3 (11)	11.6 (9)	10.3 (12)	18.4 (14)	22.2
Lanatoside C	11	2.1 (10)	3.0 (6)	6.2 (6)	11.4 (11)	18.8 (11)	0.0
<i>Lanatoside Delayed</i>							
Control period	21	>17.1 (16)	>17.1 (16)	>17.1 (16)			
After lanatoside	21	3.1 (16)	3.0 (13)	7.3 (11)	10.4 (13)	19.7 (12)	23.8
VENOUS PRESSURE AURICULAR FIBRILLATION							
>15 cm. of water	67	3.4 (47)	2.3 (38)	8.0 (40)	15.6 (34)	25.7 (30)	22.4
<15 cm. of water	35	2.8 (8)	2.3 (13)	10.5 (13)	15.2 (24)	23.9 (21)	11.4

This is a summary of data previously obtained from 188 patients with congestive heart failure. None of these patients had taken digitalis for at least three weeks before hospital admission, and all received lanatoside C within twelve to twenty-four hours after entering the hospital except in the Lanatoside Delayed series. Patients in this series were given the drug after an average of seventeen days in the hospital without digitalis therapy. The numbers within parentheses indicate the total number of cases from which each average used in the statistical analysis was obtained. The average number of days is reckoned from the time of admission to the hospital in all cases except in the Lanatoside Delayed series. In the latter, the average number of days is computed from the time the administration of the drug was begun. The control group of patients were not given digitalis at any time during their hospital stay. Reprinted from the AM. HEART J. 21: 138, 1941.

Ten of the thirteen patients with auricular fibrillation responded equally well to the intravenous administration of lanatoside C, whether the heart rate was 140 or 90 (Table II). Four had rates between 120 and 140; six had rates between 100 and 120; and two had rates between 90 and 100. One patient with an initial apical rate of 60 showed marked improvement following administration of the drug, as his case history illustrates:

O. W., a 63-year-old colored man with a history of hypertensive heart disease of six years' duration, was admitted complaining of increasing dyspnea, orthopnea, and edema of thirty days' duration. He stated that he had been taking 0.1 and 0.3 Gm. of folia digitalis on alternate days for a year. He appeared moderately dyspneic, orthopneic, and cyanotic, and râles were heard at both lung bases. His heart was enlarged; the rate was 60 beats per minute; and the rhythm was apparently regular. There was an apical systolic murmur. The blood pressure was 180/100; the liver was enlarged and tender; and there was a 2 plus pitting edema of both extremities. He was given 0.8 mg. of lanatoside C intravenously and responded within ten days with disappearance of the signs and symptoms of congestive heart failure. An electrocardiogram taken shortly before the drug was administered showed auricular fibrillation which had not been detected during physical examination. This patient manifested no signs of digitalis intoxication.

Except in this one instance, we did not give patients with auricular fibrillation and apical rates below 90 lanatoside C intravenously. We might have used the atropine sulfate test described by Gold and his co-workers⁴ to aid in determining if such patients should be given lanatoside C. These investigators state that an acceleration of more than 15 to 20 beats per minute in the heart rate within fifteen to thirty minutes after the injection of 2 mg. of atropine sulfate indicates that the optimal dosage of digitalis has not been administered. The control of the heart rates of patients with auricular fibrillation on maintenance doses of digitalis is twofold. When the heart rate accelerates following atropine, this indicates that vagal stimulation is responsible for the slow heart rate. In the adequately digitalized patient with auricular fibrillation, the heart rate fails to increase following the injection of atropine because digitalis is acting not only upon the vagus but also upon the myocardium itself.

The five patients who are designated in the charts as having shown no improvement failed to evince persistent clearing of their heart failure after twenty-five to fifty days. All were then given diuretics in addition to digitalis. These patients were discharged, or deserted, with minimal but definite evidence of persistent decompensation although they were much improved. They were followed in the clinic and were advised to take 0.2 to 0.3 Gm. of folia digitalis daily. This enabled them to stay at home for long periods before their symptoms again forced them into the hospital. Most cardiologists are familiar with the problem presented by this type of patient who is never free of the signs and symptoms of congestive heart failure, but who, with a minimum of physical activity, can remain fairly comfortable at home while taking digitalis.

Of forty-four patients who had electrocardiograms taken before and after the administration of lanatoside C, twenty-four showed "digitalis effect" before the drug was given. The electrocardiographic evidence of digitalis was more pronounced in some instances after lanatoside C had been given, and the effect on the ventricular gradient of these patients is under study. The twenty other patients showed electrocardiographic effects only after receiving lanatoside C. At present it is our belief that electrocardiographic evidence of digitalis intake is not an index of maximal therapeutic dosage of the drug.

Only one of the sixty-two patients evidenced a toxic reaction to the intravenous administration of lanatoside C. This patient was a 64-year-old colored man who had taken digitalis intermittently for seventeen years. At the time of this admission, he gave a history of six weeks' progressive distress from dyspnea, orthopnea, and swelling of the legs and abdomen. He stated that he had been taking 0.1 Gm. of folia digitalis daily. He was dyspneic, orthopneic, and cyanotic, his neck veins were distended, and râles were heard at both lung bases. On the right, an area of dullness extending from the tenth to the sixth rib was noted. His heart was enlarged; the rate was 96; and the rhythm was regular. A systolic murmur was heard over the entire precordium; the pulmonic second sound was greater than the aortic second sound; and the blood pressure was 120/90. The liver was felt 8 cm. below the costal margin in the midclavicular line, and there was a 2 plus pitting edema of the extremities. His electrocardiogram showed left bundle branch block and evidence of digitalis effect.

He was given 1.2 mg. of lanatoside C and within thirty minutes developed nausea, emesis, blurred vision, extrasystoles, and pulsus bigeminus. He was then given 2 mg. of atropine sulfate intravenously in an attempt to counteract these effects,⁵ and thirty-six hours later most of the toxic manifestations had disappeared.

It was later learned from the patient's wife that, instead of taking 0.1 Gm. of *folia digitalis* daily, as he had told us, he had in reality been getting 0.5 to 0.7 Gm. orally for seven days before his admission to the hospital, and had "lost weight" and "looked better" during that week. Had the true history been known, this toxic reaction would not have occurred, since no one would attempt intravenous digitalization of a patient already taking such large amounts of *digitalis*.

Of the sixty-two patients, eleven or 17.7 per cent died. This mortality is relatively small if compared with that previously observed² in a study of patients who were not taking *digitalis* when their heart failure occurred. In Table IV, from this previous study, it will be seen that, of fifty-two patients with regular sinus rhythm, 25.9 per cent died and, of sixty-seven patients with auricular fibrillation, 22.4 per cent died. All these patients had initial venous pressures above 15 cm. of water, as did the sixty-two patients currently reported.

Nine of the eleven patients died four to thirty days (average fourteen days) after the intravenous administration of lanatoside C, and it is unlikely that injection of the drug had any relation to the cause of death. Two patients died eighteen hours after intravenous administration of 0.8 mg. of lanatoside C; one of these had a cerebrovascular accident, the other expired in his sleep with no known pre-agonal episode. It is possible that the death of this patient might be ascribed in part to the administration of lanatoside C, but it is equally likely that it was unrelated to the drug.

DISCUSSION

The lack of toxic reactions and the definite evidence of improvement following the intravenous administration of lanatoside C to patients taking maintenance doses of *folia digitalis* before and during the development of congestive heart failure suggest several conclusions. Since the rate of improvement was more rapid than that to be expected from bed rest alone, it seems obvious that these patients were not receiving adequate therapeutic amounts of *digitalis*. A combination of factors may explain the tolerance of these patients to the intravenous administration of lanatoside C—the need for more *digitalis* when heart failure occurs, no matter what the precipitating cause, plus the possibility that the destruction and elimination of the *digitalis* accumulated during the previous period of "digitalization" contributed to the onset of congestive failure.

From our results, it would seem to be reasonably safe and usually of therapeutic benefit to give 0.4 to 0.8 mg. of lanatoside C intravenously to patients who develop congestive heart failure while taking maintenance doses of from 0.1 to 0.3 Gm. of *folia digitalis*.

Finally, this study indicates that the mere finding of "digitalis effect" in the electrocardiogram is apparently not proof that the patient is receiving adequate therapeutic doses of the drug.

CONCLUSIONS

1. The intravenous administration of from one-half to the full digitalizing dose of lanatoside C to patients developing congestive heart failure while taking maintenance doses of *Digitalis purpurea* was followed by definite improvement in forty-six of the sixty-two patients so treated.

2. Objective evidence of improvement was shown by thirty-six of forty-nine patients with regular sinus rhythm and by ten of thirteen patients with auricular fibrillation.

3. There was only one toxic reaction among the sixty-two patients.
4. The presence of electrocardiographic evidence of "digitalis effect" is not proof that therapeutic amounts of digitalis are present in the body.
5. The mortality of the patients studied was no greater than that previously observed in a group of patients with heart failure of comparable severity who had not been taking digitalis within three weeks prior to intravenous digitalization.
6. None of the deaths occurring during this investigation could be attributed to the intravenous administration of lanatoside C.

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ADDENDUM

Since submission of this manuscript, thirty-five patients with regular sinus rhythm and fifteen patients with auricular fibrillation have been added to the series. There were no toxic manifestations in the patients with auricular fibrillation; six of the patients with regular sinus rhythm developed transient toxic reactions. Thus, of 104 patients with regular sinus rhythm, seven, or 6.7 per cent, developed nausea, emesis, and occasional extrasystoles. None of the patients with auricular fibrillation experienced toxic reactions, and no deaths could be attributed to the administration of the drug.

THE DIFFERENTIATION OF NORMAL FROM ABNORMAL Q WAVES

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ALTHOUGH analysis of each of the deflections of the QRS complex has always interested electrocardiographers, the criteria of Pardee and others^{1, 2, 3} for the differentiation of normal from abnormal Q waves, and the importance of initial QRS deflections in the diagnosis of myocardial infarction⁴ have served to stimulate search for the mechanisms responsible for both normal and abnormal Q waves. Part of the difficulties encountered in the study of the Q wave has centered around the definition of Q. As generally interpreted, the Q wave is an initial downward deflection, followed by an upward deflection, in any lead. However, in many cases, especially in Lead III, a small, and sometimes insignificant, upward deflection can be found preceding the main downward deflection. Many observers have ignored this initial upward deflection in their studies and have called the main downstroke Q.

For the purposes of this paper, the Q wave shall be defined as an initial downstroke. If this deflection is preceded by an upstroke, no matter how small, so long as it is visible with the naked eye, this initial upstroke is an R wave and the downstroke which follows is an S deflection. If the QRS complex consists only of a downstroke, this may be labeled a QS wave, but we shall analyze it in the same manner as the ordinary Q wave.

Another difficulty which is encountered in study of the Q wave lies in the fact that the initial downstroke may be produced by many factors. In the standard leads, which record the difference between the potentials at two extremities, the record is taken in such a manner that when the initial potential of the right arm is relatively positive to the initial potentials at the left arm and left leg, the initial deflections in Leads I and II will be downward. This initial downstroke is, of course, a Q wave. In Lead III, a Q deflection is produced when the initial potential at the left arm is relatively positive to the initial potential at the left leg. Since this is so, a Q wave in any of the standard leads may be produced by five different combinations of potential at the two extremities. For example, Q₁ may be produced by: (1) An initial negative potential at the left leg and an initial positive potential at the left arm, (2) An initial negative potential at the left leg and an initial zero potential at the left arm, (3) An initial zero potential at the left leg and an initial positive potential at the left arm, (4) An initial positive potential at the left leg and an initial positive potential at the left arm (in such a case the left arm potential is more positive than that at the left leg), and (5) An initial negative potential at the left leg and an initial negative potential at the left arm (in such a case the left arm potential is less negative than that at the left leg). On theoretical analysis, therefore, we reach the interesting conclusion that a Q wave in a standard lead may occur *even if the initial potentials at both extremities are positive*.

It therefore becomes obvious that study of the Q wave by means of standard leads leaves much to be desired. Fortunately we are not limited to the

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use of standard leads alone, nor to theoretical analysis of the potentials at each of the extremities, because, with a very simple technique, the actual unipolar extremity potentials can be recorded,⁵ and the mechanisms which produce Q waves can be more exactly studied. Fig. 1, for example, illustrates two variations in unipolar extremity lead potentials which can produce a Q₃ deflection. In Fig. 1, *a*, the Q₃ wave occurs because of an initial negative deflection in the left leg lead and an initial positive deflection in the left arm lead. However, in Fig. 1, *b*, although a Q₃ deflection is present, the initial potentials at both the left arm and left leg leads are actually positive. Because this is so, it would appear that study of the Q wave resolves itself into two problems at least: (1) an analysis of the actual potentials at each extremity which cause the various Q-wave patterns, and (2) an attempt to define the Q wave, if possible, in terms of the spread of the initial activity within the heart. We have used both these approaches in the following report.

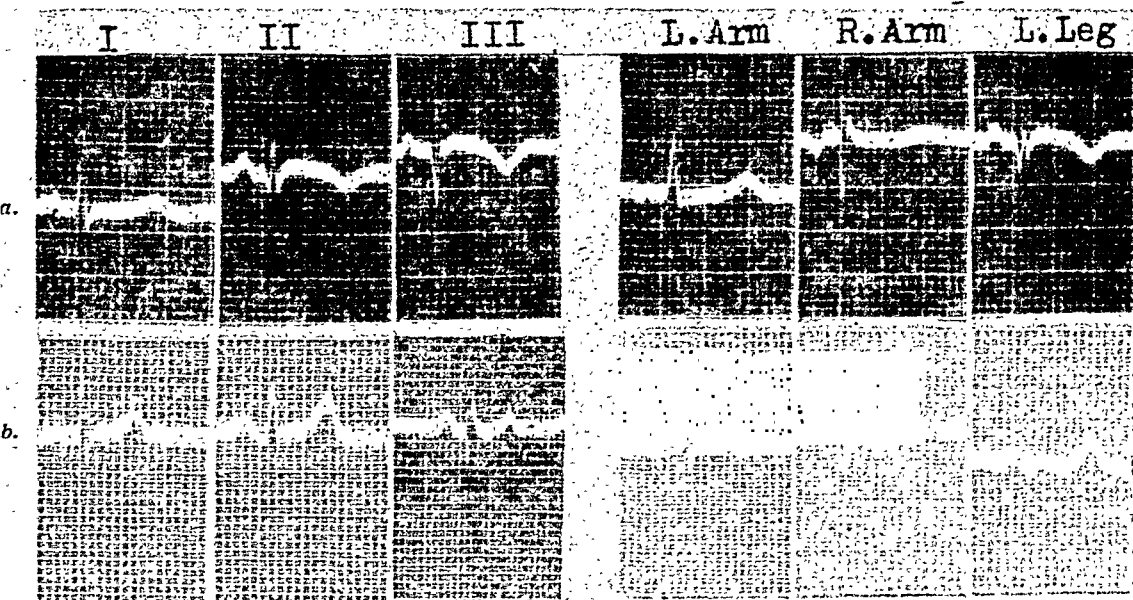


Fig. 1.—Two different mechanisms which can produce a Q₃ wave. *a*, A case of posterior infarction; N. L., male, 61 years of age. *b*, A normal heart; J. B., male, 65 years of age. L.Arm, R.Arm, and L.Leg represent unipolar extremity leads taken with the author's technique.⁵

MATERIAL AND TECHNIQUE

For this paper I reviewed the electrocardiograms of more than five hundred cases from our files. These included the records of two hundred normal subjects and patients with normal-sized hearts; two hundred patients with cardiac hypertrophy (thickening of the right or left ventricle, or both); one hundred cases of myocardial infarction; and fifty cases of bundle branch block. In most of these cases, multiple unipolar precordial leads had been taken in addition to the unipolar extremity leads and standard leads. The unipolar leads were taken with the author's indifferent electrode of zero potential,⁵ and the author's technique of obtaining augmented unipolar extremity leads was used.⁵ In addition to this, multiple unipolar leads from twenty or more points on the surface of the body were taken in seventy-five of the cases.

METHOD AND RESULTS

Although it is possible, as I pointed out, for a Q wave to appear in a standard lead, even if the initial potentials at both extremities are positive, I found as a general rule that: (a) Q₁ was usually associated with a Q wave

in the left arm lead (Q-LA), especially if a Q wave was absent in Lead III, and (b) Q_3 was usually associated with a Q wave in the left leg lead (Q-LL), especially if a Q_2 was also present. Exceptions to these rules will be found throughout the paper.

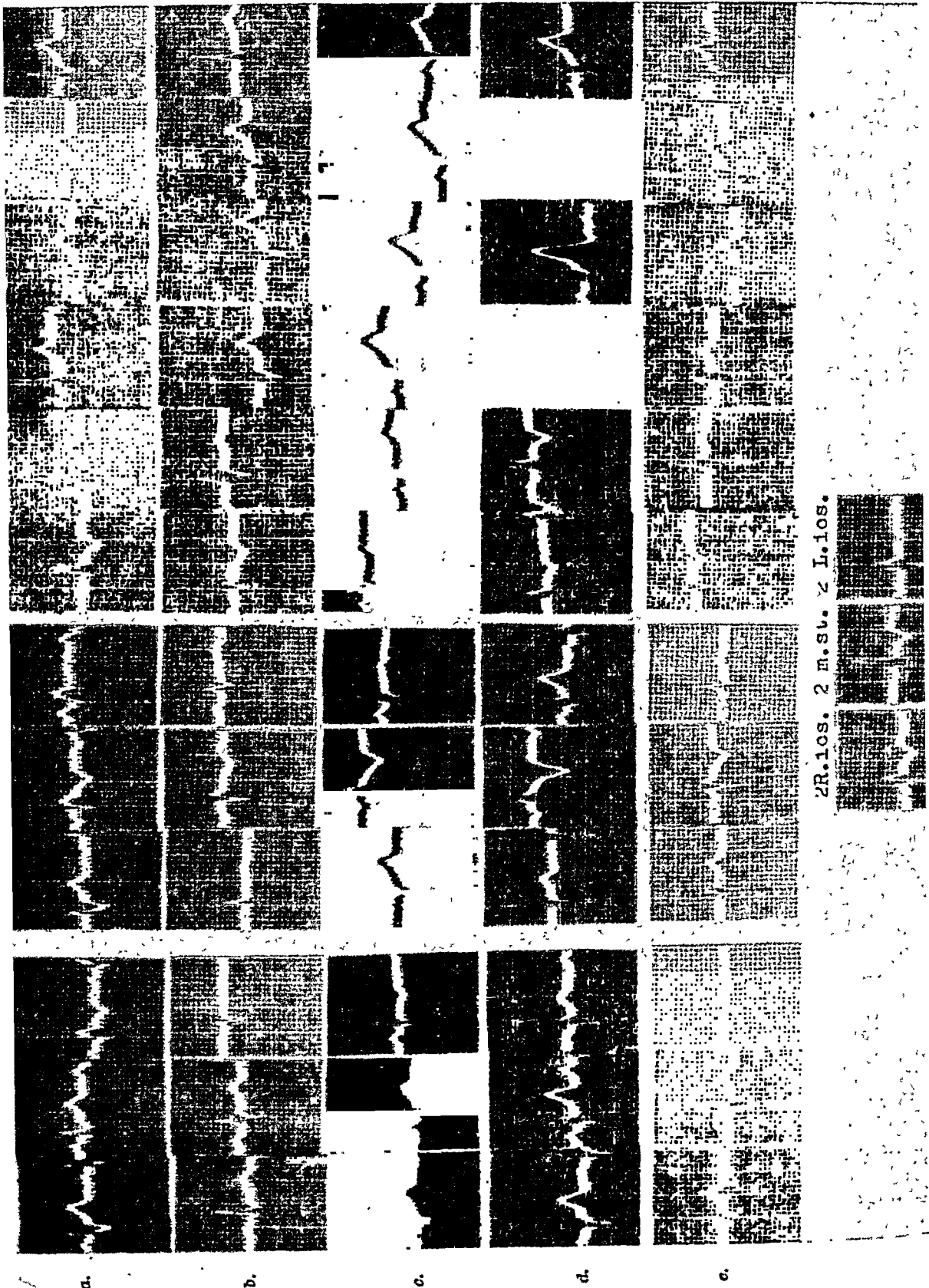
In my study of the origin of the Q wave I used a method of analyzing the QRS complex in terms of the spread of the impulse through the ventricles which depends on the following physiologic principles, which are valid when the electrical activity of the heart is studied with unipolar leads;^{6, 7} (1) An electrode facing a region to which the electrical activity is spreading will record a positive deflection. (2) An electrode facing this same region, but in the direction from which the impulse is passing, will record a negative deflection. (3) If the impulse runs at right angles to an axis formed by drawing a line from the electrode to the region of electrical activity, the electrode will not record the electrical activity.^{8, 9} (4) Within the ventricles, the electrical activity spreads from the subendocardial region outward to the epicardium of both ventricles, so that the endocardium tends to be negative throughout the entire QRS complex.^{10, 11} Statement 4 does not take into account the electrical activity of the interventricular septum because it has been assumed in the past that the impulse also spreads from the endocardium on both sides of the septum inward, thereby nullifying the electrical effects of the septum.¹²

We believe, however, that the left side of the interventricular septum is activated earlier than the right side and that the spread of the impulse through the septum from left to right is the basic cause of the Q wave in the human electrocardiogram. The following observations support such a concept:

The Relationship Between the Normal Electrocardiogram and the Patterns of Right Bundle Branch Block.—

A. Even if we assume the problem of septal activation in the normal heart to be unanswered, no one can question the fact that in cases of right bundle branch block the left side of the septum is activated earlier than the right side. Therefore a unipolar lead placed on the chest in such a position that it faces the right side of the septum will record this initial septal activity with an initial positive deflection. Similarly, a unipolar lead taken from a point on the chest facing the left side of the septum will record this initial septal activity with an initial negative deflection (Fig. 2,a). In addition to these initial deflections, the precordial leads in cases of right bundle branch block have the following characteristics:⁷ (a) Precordial leads near the sternum, which face the right side of the septum, have an M-shaped QRS complex. (b) Precordial leads which face the left side of the septum have a W-shaped QRS complex, although the initial Q wave is often small and inconspicuous. (c) Although bundle branch block is usually not considered to be present until the QRS interval exceeds 0.12 second, it is well known that cases of right bundle branch block may have a QRS interval which does not exceed 0.1 second.¹² In my series of records from normal subjects or from patients without heart disease (determined on the basis of history, physical examination, and x-ray study) I found ten cases in which the precordial leads were very similar to the patterns found in right bundle branch block. Four of these cases are illustrated in Fig. 2. An M-shaped QRS complex is present in precordial Lead V_1 (Fig. 2,b), and in Leads V_1 and V_2 (Fig. 2,c and d). A W-shaped QRS complex is present in precordial Leads V_3 , V_4 , V_5 , and V_6 (Fig. 2,b); Leads V_3 and V_6 (Fig. 2,c); and Lead V_6 (Fig. 2,d). The patterns in the standard and unipolar extremity leads can be correlated with these precordial lead patterns if one remembers that, when the heart is horizontal, the left arm lead and Lead I tend to resemble leads facing the surface

of the left ventricle; and when the heart is vertical, the left leg lead and Leads II and III tend to resemble the precordial leads facing the left ventricle.⁶ Therefore, in Figs. 2, *b*, *c*, and *d*, the left arm lead and Lead I have a Q deflection. In Fig. 2, *d*, the left leg is also facing the left ventricle, and the left leg lead and Leads II and III also have Q waves. Although an M-shaped QRS complex in



the first two precordial leads is not ordinarily seen in the normal electrocardiogram, nevertheless in cases where the first two precordial leads show the usual pattern, the M-shaped QRS complex can often be seen in unipolar leads taken higher on the anterior chest wall, such as over the sternum at the level of the second intercostal space, Fig. 2, *e*, shows such a record.

B. The histological studies of Mahaim¹³ support such a concept, as does recent interpretation of the standard leads on the basis of vector analysis.¹⁴

C. Experimental records obtained from within the ventricular cavity of dogs often exhibit a small upward deflection preceding the main negative deflection when the electrode is placed within the right ventricular cavity, and it was suggested some years ago that this small upward deflection might be due to early activation of the left side of the septum in advance of the right side.¹¹

D. A small R wave is found in human beings in precordial leads close to the sternum,* whereas in one or more of the precordial leads over the left side of the chest a small Q wave may usually be observed.

E. Finally, we may point out that a Q wave and an S wave, such as Fig. 2, *c*, shows, in the standard leads is considered one of the basic characteristics of the normal standard lead electrocardiogram.

We may therefore conclude that in a normal heart, at least, a Q wave in a unipolar lead is due to the fact that the left side of the interventricular septum is the first region of the heart to be activated. It should, however, be remembered, as I emphasized in the introduction, that if an electrode lies on the same plane as the septum, for example, the initial impulse which is passing at right angles to this plane will not be recorded by the electrode so placed. Consequently not every initial impulse, either positive or negative, even if recorded by unipolar leads, can be said to be due to septal activity. Therefore with the exception of this condition, a Q wave should be found in all unipolar leads which face the left side of the septum, and an initial positive deflection should be found in those unipolar leads which face the right side of the septum.

To theorize further, two types of unipolar leads with a Q wave can be anticipated: (1) Leads facing the endocardium of the left ventricle and the left side of the septum should display not only a Q wave but a downward main QRS deflection. Thus, the QRS complex might consist of a QS deflection. (2) Leads facing the left side of the septum and the epicardial surface of the left ventricle should display an initial Q wave due to septal activity, followed by a high R wave due to the spread of the impulse outward through the left ventricular wall. In an attempt to confirm this concept I studied the initial deflections in a series of seventy-five cases in each of which twenty or more unipolar leads had been taken from the surface of the body.

Before discussing the results, however, it should be emphasized that in all studies on the distribution of potentials from the surface of the heart to

*We do not wish to imply by this statement that the entire deflection of such an initial R wave is due to septal activity, because part of it is due to the wave of activation passing outward through the free wall of the right ventricle.¹²

Fig. 2.—Cases illustrating the relations between normal electrocardiograms and the pattern of right bundle branch block. *a*, right bundle branch block; R. B., female, 67 years of age. *b*, Normal heart; E. P., female, 73 years of age. *c*, Normal heart; I. H., male, 19 years of age. *d*, Normal heart; H. R., male, 12 years of age. *e*, Normal heart; P. S., female, 22 years of age. V_1 to V_6 represent unipolar precordial leads. The electrode was placed in the following positions: V_1 , fourth intercostal space to right of sternum; V_2 , fourth intercostal space on left mid-clavicular line; V_3 , midway on a line joining points of V_2 and V_4 , fifth intercostal space on left mid-clavicular line; V_4 , continuation of fifth intercostal space on left anterior axillary line; V_5 , continuation of fifth intercostal space on left midaxillary line. Three other unipolar leads are shown in *c*: $2R.ics.$, electrode on second right intercostal space on mid-clavicular line; $2m.st.$, electrode over sternum at level of second intercostal space; $2L.ics.$, electrode on second left intercostal space on mid-clavicular line.

the surface of the body, variations in the position of the heart within the thorax are accompanied by marked variations in the distribution of the potentials on the surface of the body and the extremities. The effect of a horizontal or vertical heart on the extremity patterns has already been mentioned briefly. This can now be further discussed. The position of the heart may vary because of rotation around any one or more of the following three axes: (A) Rotation around an anteroposterior axis. This causes the long axis of the heart to become horizontal or vertical. (B) Rotation around the long axis of the heart. This causes the right ventricle to move anteriorly, or to the right. (C) Rotation around a transverse axis. This causes the apex of the heart to be pushed forward or backward. Although a detailed description of the effects of rotation on the distribution of potentials over the surface of the body will not be given, the effects of such rotations on the extremity leads can be briefly sketched, although it must be remembered that countless variations may exist, determined not only by the position of the heart, but also by the size and shape of the thorax, and other factors.

1. When the heart lies vertically, it is usually also rotated clockwise around its long axis and the following occurs: (a) The left arm lead tends to face the endocardium of the heart and the right side of the interventricular septum. Its initial deflection should be upward, followed by an S. (b) The right arm lead tends to face the endocardium of the heart and the right side of the septum. Its initial deflection therefore also should be upward, followed by an S. (c) The left leg lead faces the left side of the septum and the epicardial surface of the left ventricle. A Q wave followed by a high R wave should occur. *A heart in such a position should cause the pattern in the standard leads, described as right axis deviation, with Q_2 and Q_3 waves. If the clockwise rotation around the long axis becomes marked, the right arm lead may lie on the same plane as the septum or actually face the left side of the septum, and the initial deflection will be downward.

2. When the heart is horizontal, it is usually rotated counterclockwise around its long axis, and the following should occur: (a) The left arm lead now faces the left side of the septum and the epicardial surface of the left ventricle. A Q wave followed by a high R wave should be present. (b) The right arm lead continues to face the right side of the septum and the endocardium. Its initial deflection should be upward, followed by an S wave. (c) The left leg lead faces the right side of the septum and the epicardial surface of the right ventricle. Its initial deflection should be upward, followed by an S wave.*

3. When the apex is pushed forward, the following occurs: (a) The left arm lead tends to resemble potentials from the anterior surface of the ventricles. The initial deflection will vary, depending on whether the left arm is facing more of the right ventricle than the left, and on other factors. (b) The right arm lead tends to be similar to unipolar precordial leads near the sternum. The initial deflection will be upward followed by a deep S wave. (c) The left leg lead tends to record potentials from the epicardial surface of the left ventricle. A Q wave followed by an R deflection should occur.

4. When the apex of the heart is pushed backward, the following occurs: (a) The left arm lead tends to resemble unipolar leads, ordinarily derived from the left upper back. In such leads (on the basis of my observations) the

*The S wave is due to the fact that the right ventricle is smaller than the left ventricle. Thus, the potentials developed within it are weaker than those developed by the left ventricle, and an electrode, although facing the epicardial surface of the right ventricle, is also facing the tail of the wave passing outward through the left ventricle, causing the main deflection to be downward.⁵

Q wave is usually deep and the R deflection is of variable size. (b) The right arm lead also tends to resemble unipolar leads ordinarily obtained from the right upper back. Such leads often have a deep Q wave followed by a high R deflection. (c) The left leg lead tends to resemble potentials from the epicardial surface of the right ventricle. The initial deflection should be upward followed by an S wave.

With these facts in mind, the results can now be analyzed. Fig. 3 illustrates the distribution of potential over the surface of the body in a normal subject. This record and Fig. 2,d, are from the same patient. A small Q wave, followed by a high R deflection, can be seen in both the left arm and left leg leads (Fig. 2,d), showing that the position of the heart is neither fully vertical nor fully horizontal. Consequently the regions of the surface of the body facing the left ventricle are extensive and unipolar leads (Fig. 3) from the left upper chest (2 *L.ics.*), the abdominal wall (*RUA* and *LUA*), and lower back (*LB.*) show a Q deflection and high R wave. A small R deflection followed by a deep S wave is found, on the other hand, in unipolar leads from the right upper chest wall. The unipolar leads from the back in this case illustrate particularly well the transition of the two types of Q-wave patterns described above. The upper scapular lead (*u.Sc.*) is completely negative. At the level of the scapular angles

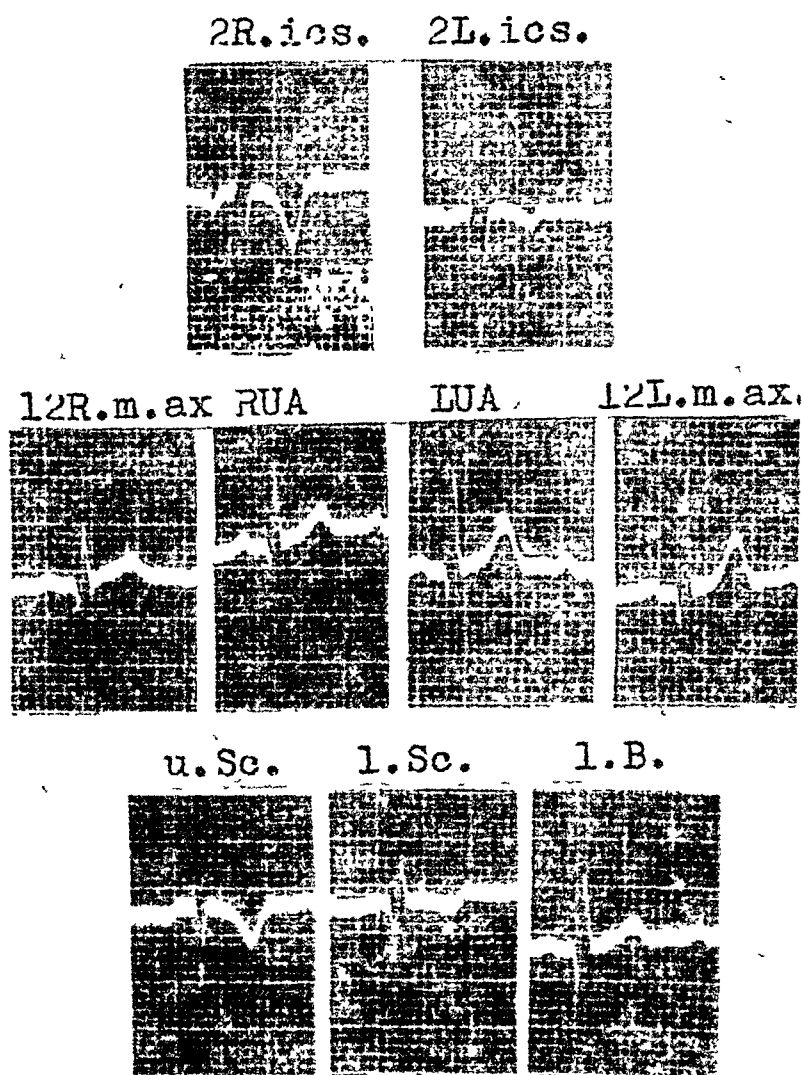


Fig. 3.—Unipolar leads in a normal subject. The standard, unipolar extremity, and precordial leads of this subject are illustrated in Fig. 2,a. The other unipolar leads shown are: 12*R.m.ax.*, electrode on right midaxillary line at level of twelfth intercostal space; *RUA*, electrode on continuation of right mid-clavicular line at level of lowest border of ribs; *LUA*, like *RUA*, but on left side; 12*L.m.ax.*, like 12*R.m.ax.*, but on left side; 2*R.ics.*, electrode on second right intercostal space on mid-clavicular line; 2*L.ics.*, like 2*R.ics.*, but on left side; *u.Sc.*, electrode on back at level of base of spines of scapulae, just to the left of the midline; *1.Sc.*, electrode on back at level of angles of scapulae, just to the left of the midline; *1.B.*, electrode on the back at level of twelfth rib, just to the left of the midline.

it is biphasic and consists of a deep Q wave and high R deflection (*L.Sc.*). The T wave is still negative here. At the level of the lower back (*L.B.*), although the Q wave is still deep, the R deflection has become tall and the T wave has become positive. This pattern is similar to the left leg lead and Lead III. This case also illustrates another important characteristic of the Q waves obtained from different portions of the body. When the Q is recorded by a lead which faces the epicardial surface of the left ventricle, its duration* is shorter than in those leads facing the endocardium of the left ventricle. In this case, as in the other cases with a normal QRS interval in the series, the duration of the Q wave in the back leads was 0.04 to 0.06 second. This approximates the entire duration of the QRS complex. However, in the leads facing the epicardial surface of the left ventricle, the duration of the Q wave was less than 0.04 second. This will be further discussed in a later section of the paper.

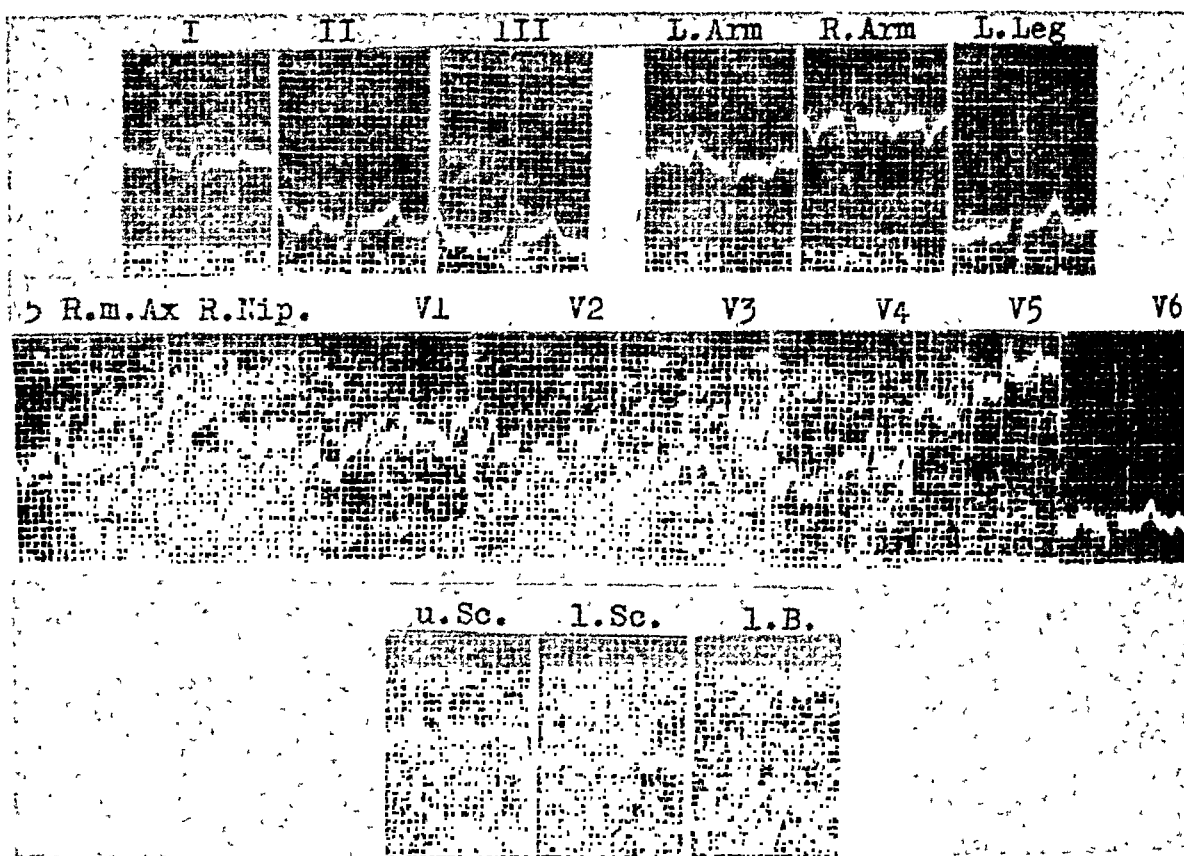


Fig. 4.—A vertical heart with right axis deviation but without Q_2 and Q_3 . A case of mitral stenosis and insufficiency; G. M., male, 12 years of age. The patient had been digitalized. *5R.m.Ax.*, electrode on right midaxillary line at level of fifth intercostal space; *R.Nip.*, electrode over right nipple. For explanation of the other leads, see captions of Figs. 3 and 4.

THE Q WAVES IN CASES IN WHICH THE HEART IS VERTICAL

If, as we have stated, right axis deviation is due to a vertical heart, the left ventricle will face the left leg, and the left leg lead and Leads II and III should have a Q wave. We studied one hundred forty cases showing right axis deviation with this in mind. These cases included patients with normal-sized hearts, and patients with left ventricular hypertrophy as well as those with right ventricular hypertrophy. A Q wave was found in one hundred thirty cases in the left leg lead, in Lead III, and, in most of the cases, in Lead II. In only ten cases was a Q wave absent in the left leg lead and Leads II and III. Careful unipolar lead studies were made in six of these ten cases, and

*The duration of the Q wave is the interval between its downstroke and upstroke. It is measured at the upper level of the string image.

in all of them were found a Q wave and a high R deflection, either posteriorly over the lower back, or in the left axilla. This, in itself, indicates that the position of the heart in such cases is different from that which occurs in the ordinary cases of right axis deviation.

Fig. 4 illustrates why a $Q_{2,3}$ is absent in such cases. This is the record of a 12-year-old boy with rheumatic heart disease and mitral stenosis. He was in congestive heart failure and was receiving digitalis. Although right axis deviation is present, there is no Q wave in either the left leg lead or Leads II and III, although a small Q wave with a high R deflection can be seen in precordial Lead V_6 , and in all the unipolar leads taken from the back. The reason for this becomes clear if we study the right arm lead. A deep Q deflection with a high R wave is present. This, as was previously mentioned, is an indication

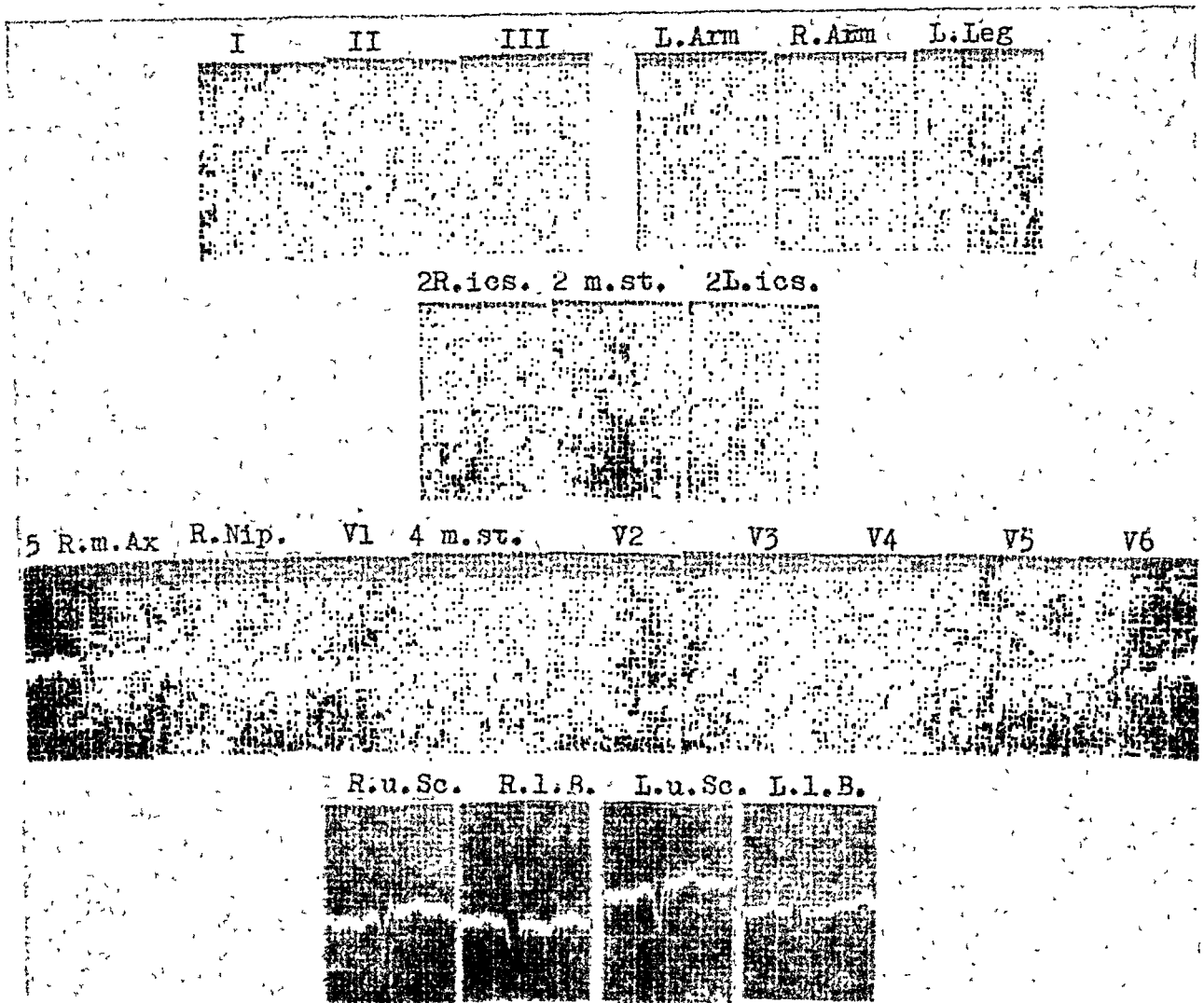


Fig. 5.—A vertical heart with right axis deviation but without a Q_2 and Q_3 . A case of interauricular septal defect; J. D., female, 36 years of age. Patient was receiving no medication. 4m.st., electrode over sternum at level of fourth intercostal space. R. and L.u.Sc., electrodes at bases of spines of scapulae. For explanation of the other leads, see captions of Figs. 3 and 4. R. and L.L.B., electrodes on back in twelfth intercostal space directly under the angles of the scapulae.

that the apex of the heart has been pushed backward. In such a case, in spite of the right axis deviation and vertical position of the heart, the left leg lead will tend to face the right ventricle instead of the left ventricle. Therefore, no Q waves should be expected in the left leg lead or Leads II and III. The high amplitudes of the R waves in these leads, in this case, are due to the right ventricular hypertrophy which was present.

There is another type of Q wave which occurs occasionally in cases of right ventricular hypertrophy. This occurs with a high R deflection and is

found in precordial leads near the sternum. Although the precordial leads of Fig. 4 did not show this, Fig. 5 illustrates a case of right ventricular hypertrophy in which a Q did occur in precordial Lead V_1 . This was the record of a 36-year-old woman with an interauricular septal defect. She was not receiving any medication. In this case, the unipolar leads which were taken across the chest illustrate well the development of the small initial upward deflection ordinarily noted, and the origin of the Q wave. Precordial Lead V_1 begins with a deep Q deflection. This is similar to unipolar leads from points over the right nipple (*R. Nip.*); the right midaxillary line in the fifth intercostal space (*5R. m.Ax.*); the second right intercostal space on the mid-clavicular line (*2R.ics.*); and the right arm lead. However, a precordial lead over the mid-sternum at the level of the fourth intercostal space (*4 m.st.*) has a small initial upward deflection. This can also be observed in precordial Leads V_2 , V_3 , V_4 , and even V_5 , where it appears as a slurring on the large main upstroke of the QRS complex. Similarly, although a unipolar lead from the second right intercostal space on the mid-clavicular line (*2R.ics.*) has a Q wave, the unipolar lead overlying the sternum at this level (*2 m.st.*) has a characteristic initial upstroke. When this record is compared to Fig. 4 and Fig. 3 (which is from a normal subject), the Q wave in Fig. 4 was found only in the right arm lead and the right midaxillary lead (*5R.m.Ax.*); and in Fig. 3, a deep Q deflection was found only in the right arm lead and in the region of the midback.

On the basis of these observations and our detailed study of twenty similar cases of right ventricular hypertrophy,¹⁵ we can describe the origin of the Q wave in such cases. With right ventricular hypertrophy, the position of the heart is usually vertical; and clockwise rotation of the heart around its long axis ordinarily occurs. If this clockwise rotation becomes marked, or if the large right ventricle displaces the position of the interventricular septum sufficiently, potentials which ordinarily would be projected to the right midback or the right midaxillary line, are projected anteriorly and a Q wave (which ordinarily is found in such regions) results. The Q deflection is therefore due to the fact that the electrode is either lying on the same plane as the interventricular septum or is actually facing the left side of the septum, because of the marked rotation, or displacement of the septum. The final R wave may be due to the passage of the impulse outward through either the right or left ventricular wall or through both. The Q in the right arm lead is due either to the marked clockwise rotation of the heart around its long axis, or to backward displacement of the apex, as was previously mentioned, or to a combination of both factors. Further proof that backward displacement of the apex has occurred can also be found in the standard and unipolar extremity leads in Fig. 5. Careful examination of Lead III and the left leg lead show that the initial deflection is not a Q wave but is upward, in spite of the fact that right axis deviation exists. Comparison of the left leg lead with the precordial leads indicates the marked similarity between it and precordial Lead V_2 . This occurs, as has already been stated, when the apex of the heart has been displaced backward, so that the left leg lead records a pattern which can be found in precordial leads overlying the right ventricle, rather than the left ventricle.

Occasionally in cases of right ventricular hypertrophy a deep Q_1 occurs. There was one such case in the series. It is illustrated in Fig. 6. This is the record of a 36-year-old man with mitral stenosis, massive enlargement of the left auricle, and marked pleural effusion. Examination of Fig. 6 reveals the similarity between the right arm lead and unipolar leads from the right upper

chest (2R.ics.) and precordial leads near the sternum. All these leads have an initial R wave. On the other hand, precordial Leads V_5 and V_6 , the left upper abdominal lead (not shown), the left leg lead, and the back leads have a small Q wave. The significance of the deep Q deflection in the left arm lead (and in Lead I) can be appreciated by comparing the left arm pattern with the record obtained from the second left intercostal space on the mid-clavicular line (2L.ics.). The two leads are similar except that the small R deflection present in the second left intercostal space disappears in the left arm lead. This can be explained by the fact that the left arm lead lies on the same plane as the interventricular septum. From the distribution of potentials in this case and the similarity of the right arm lead to the right anterior chest potentials, rather than to potentials from the back, and the similarity of the left leg lead to the precordial Lead V_6 , we can assume that the apex in this case has been pushed forward. This is unusual in cases of right ventricular hypertrophy.

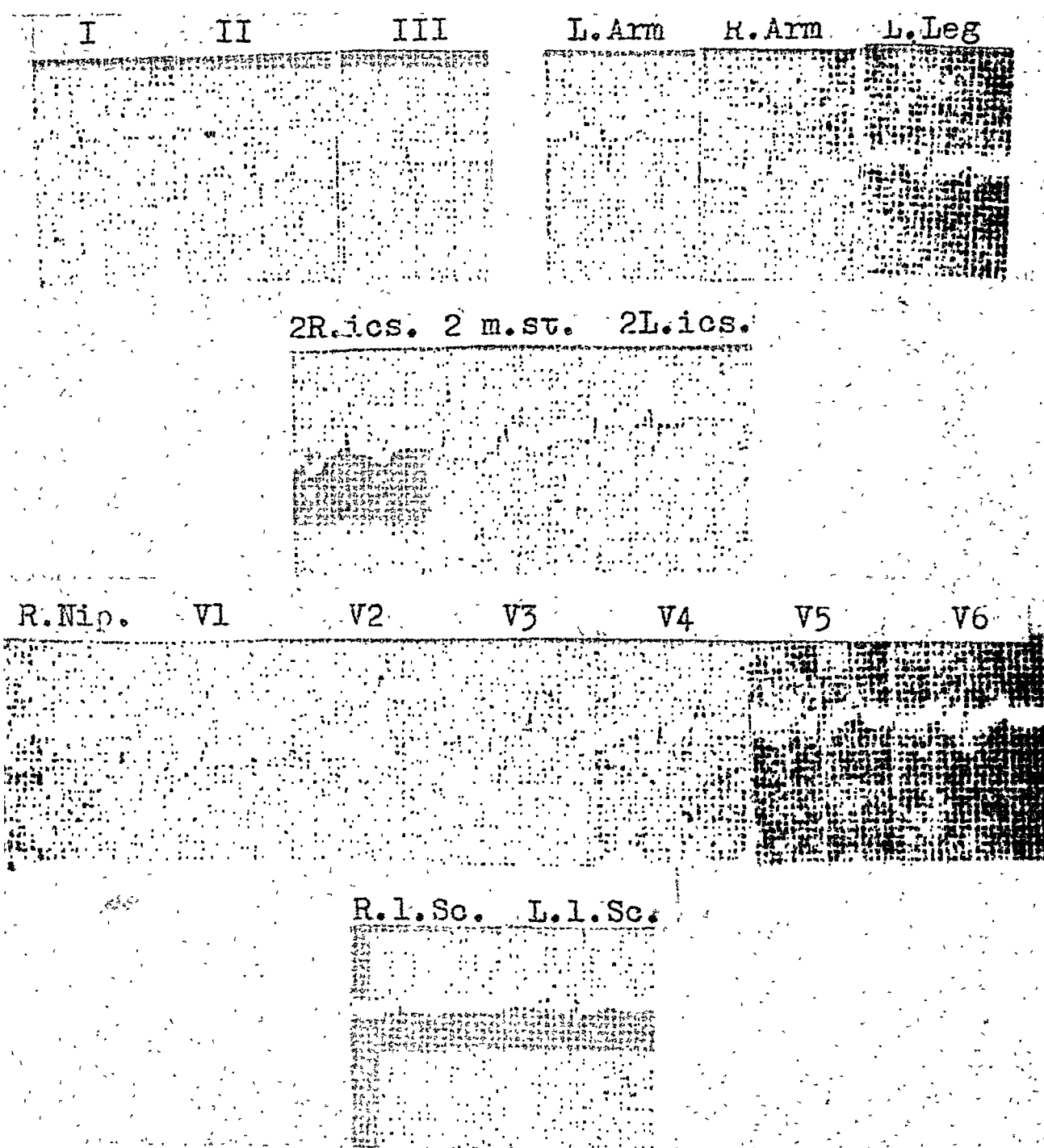


Fig. 6.—A vertical heart with a deep QS. A case of mitral stenosis. H. B., 36 years of age. Patient had been digitalized. For explanation of the leads, see captions of Figs. 3, 4, and 5.

THE Q WAVE IN CASES IN WHICH THE HEART LIES HORIZONTALLY

If, as I have stated, left axis deviation is due to a horizontal heart, the left ventricle faces the left arm lead and the left arm lead and Lead I should have a Q wave, and a high R deflection. A series of one hundred twenty cases showing left axis deviation in the standard leads were studied. These included persons with normal hearts, patients with enlargement of the left ventricle, and patients with enlargement of both the right and left ventricles. In one hundred seven cases, a Q_1 wave and a Q deflection in the left arm lead were found. In eight other cases, although a Q_1 wave was absent, a Q deflection was present in the left arm lead (Fig. 7,a). In five cases, although the pattern in the standard leads was that of left axis deviation, a Q wave was absent in Lead I and the left arm lead, but a Q deflection was found in the left leg lead (Fig. 7,b). Such cases had a very deep Q_3 deflection. Although we have not made sufficient studies in such cases to accurately describe the position of these hearts, it would appear that some degree of unusual rotation has occurred.

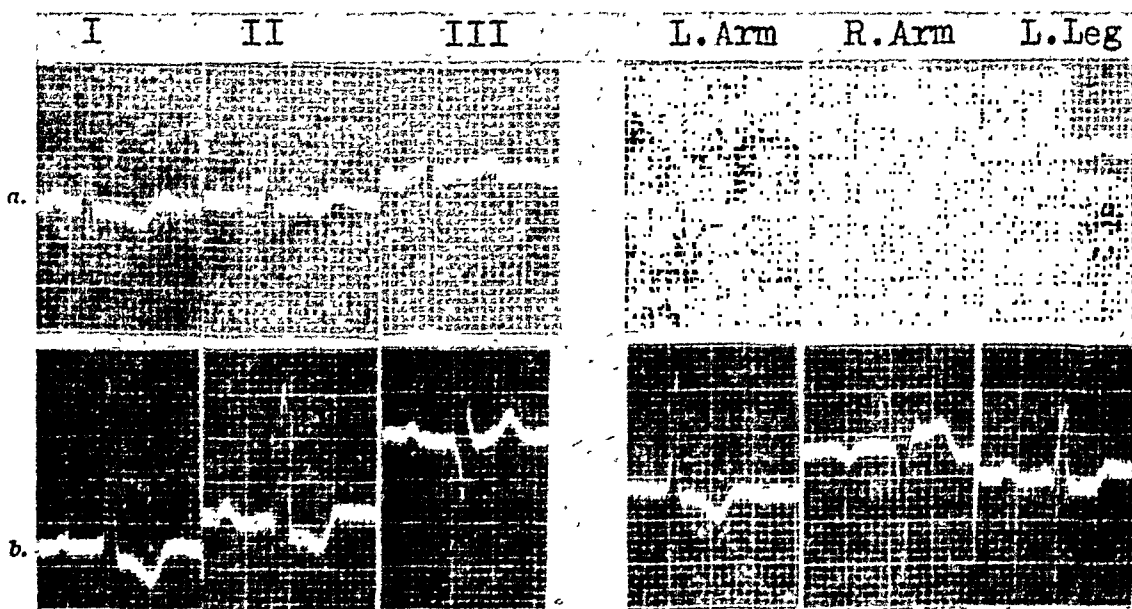


Fig. 7.—Two cases with horizontal hearts. For explanation see text.

THE Q WAVE IN CASES OF MYOCARDIAL INFARCTION

If the Q wave is due to early activation of the left side of the septum, variations in the distribution of the Q wave which are due to the position of the heart should be found in cases of myocardial infarction in a manner similar to that which occurs in the normal and hypertrophied heart. There is, however, another mechanism by which Q waves may occur after infarction. Such Q waves are deep, and the entire QRS complex may consist of a QS deflection. Such Q waves are found when the infarct tends to involve the entire thickness of the ventricular wall; they are recorded by unipolar leads which overlie or face the infarct. The explanation which has been advanced for the presence of these deep Q waves is that the large area of infarcted tissue is without electrical activity and acts like a window in the ventricular wall so that an electrode, overlying the infarct, records potentials similar to an electrode which would be placed within the ventricular cavity. Such Q waves we have noted also have an increased duration, similar to the Q waves which are normally recorded from leads facing the ventricular cavity. This concept, of course, assumes that the ventricular cavity is negative at the beginning of the QRS

complex. However, if, as I have stated, the left side of the septum is activated before the right side in a case with normal conduction or with right bundle branch block, only the cavity of the left ventricle will be negative when the QRS begins. Therefore, even if an electrode were placed over an extensive infarct of the right ventricular wall, Q waves should not be recorded from such leads. If the infarct is small, the initial deflections of the QRS complex, before and after the infarction, remain more or less unchanged, and deep Q waves do not develop.¹⁶ Irrespective of whether Q waves are, or are not, present in a case of infarction, the most characteristic sign of an acute infarct is the presence of an elevation of the RS-T segment, fusing with the T wave, which is coved. This pattern is also found in unipolar leads which overlie, or face, the infarct.

We can, therefore, summarize the Q-wave patterns which may be anticipated in a case of myocardial infarction, in the following way: (1) With infarction of the right ventricle or of a region which is near the plane of the interventricular septum, a unipolar lead overlying the infarct will record RS-T elevation without a Q wave, even though the size of the infarct may be extensive. (2) With infarction of the anterior surface of the left ventricle, a unipolar lead overlying the infarct may record the characteristic RS-T elevation due to the infarct and a small Q wave, which is a normal phenomenon. (3) Infarction of the anterior or anterolateral surface of the left ventricle, involving a large part of the thickness of the muscle wall, should produce a characteristic deep Q wave followed by marked RS-T elevations in unipolar leads overlying the infarct. (4) If only the subendocardial layers of muscle are infarcted and the outer layer is normal, a unipolar lead overlying the infarct will record a fairly deep Q wave followed by an R or even an S deflection.¹² (5) Assuming that the infarct does not involve the entire surface of the left ventricle, regions should be found overlying normal muscle, in which a small normal Q wave may be recorded with a high R deflection and an upright or high T deflection (or with depression of the RS-T segment): (6) The patterns in the unipolar extremity and standard leads after infarction should depend on the position of the heart, just as in cases where the heart is normal or hypertrophied, as well as on the actual location and extent of the infarct. In other words, in a case of antero-lateral infarction of the left ventricle in a horizontal heart, the left arm lead and Lead I, which face this region, should show the characteristic Q wave and elevated RS-T complex; whereas if the heart were vertical, the left leg lead and Leads II and III, which now would face the infarcted region, should possess the characteristic Q wave and the elevated RS-T complex, in spite of the fact that the infarct was anterior. Similarly, in a case of posterior infarction, if the heart were vertical, the characteristic Q wave and elevated RS-T complex would be seen in the left leg lead and Leads II and III; whereas if the heart were horizontal, the left arm lead and Lead I would face the infarct and record a Q wave and elevated RS-T complex.

Before continuing the discussion, consideration should be given to the position of the heart in cases of infarction. I do not believe that a vertical or horizontal, normal or hypertrophied, heart occupies the same position as a vertical or horizontal heart in which infarction has occurred, because certain factors contribute to the changes in position after infarction which are different from those affecting a normal or hypertrophied heart. In the first place, a large area of muscle is no longer functioning normally, and the force of contraction of the remaining normal musculature may cause abnormal torsion of

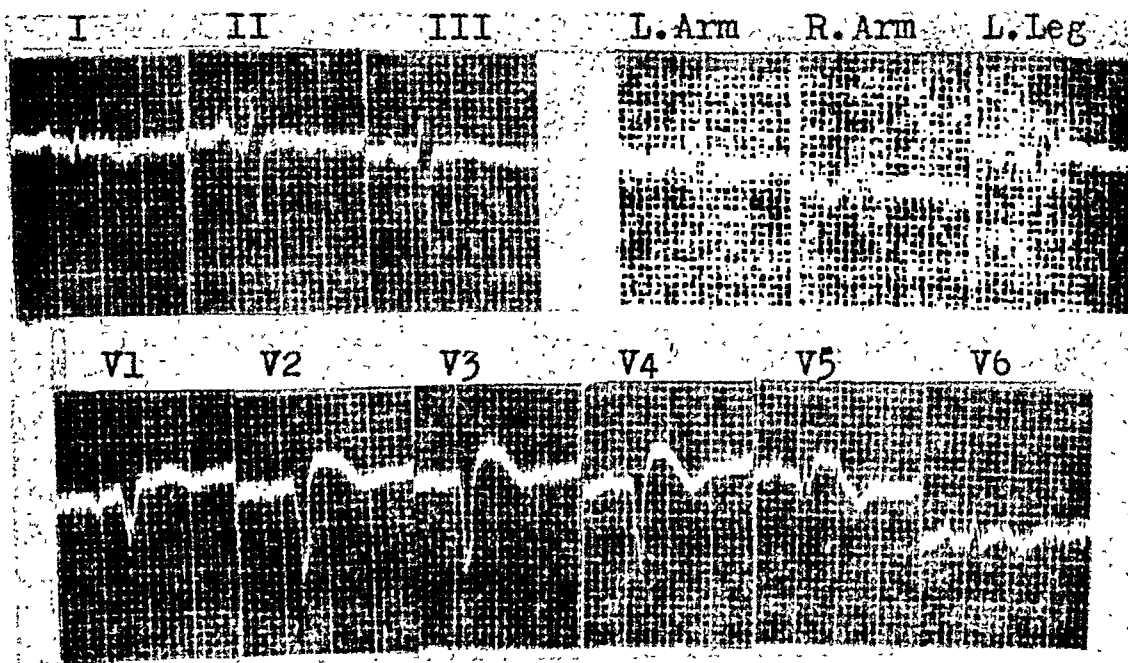


Fig. 8.—A case of anterior infarction with the heart in a horizontal position. A. F., a man, 69 years of age.

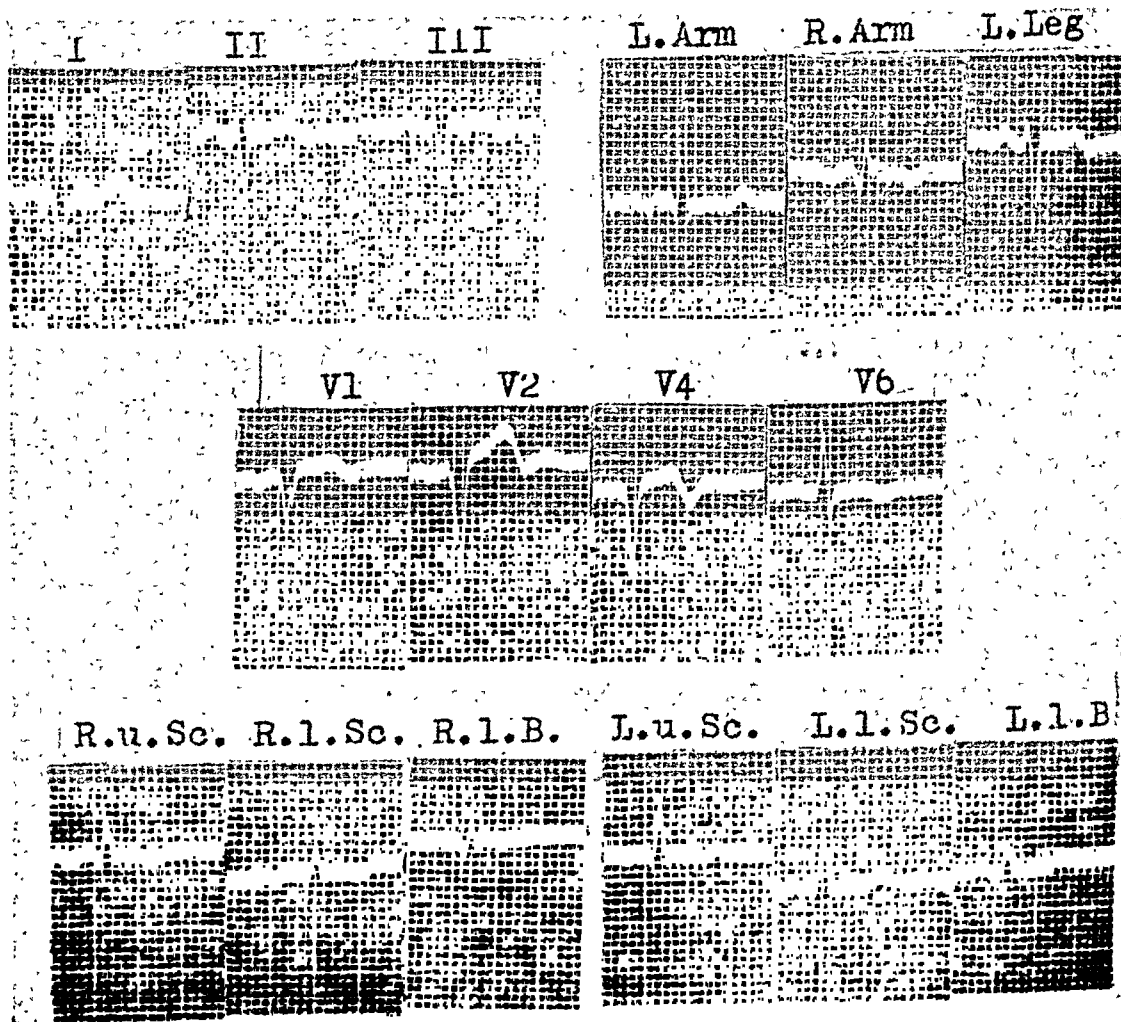


Fig. 9.—A case of anterior infarction with the heart in a horizontal position. L. Z., a man, 69 years of age. For explanation of leads see captions of Figs. 3, 4, and 5.

the heart around any of its axes. In the second place, changes in the size of the heart may occur due to abnormal cardiovascular dynamics such as a decrease in cardiac output, cardiac decompensation, localized dilatation, and other factors. Therefore, although the heart be more or less vertical or horizontal, the typical patterns of right or left axis deviation need not be always observed. The following cases illustrate the validity of these conclusions.

THE Q WAVE IN CASES OF ANTERIOR INFARCTION WITH THE HEART
LYING HORIZONTALLY

Fig. 8 is typical of records obtained after anterior infarction when the heart lies horizontally. The characteristic patterns of infarction are observed in the left arm lead and Lead I, whereas the left leg lead and Leads II and III are typical of the patterns found with a horizontal heart. The biphasic right arm potential is suggestive of the fact that the apex of the heart has been displaced backward. This would further serve to make the left leg lead face the right ventricle. Fig. 9 is the record of another case in which infarction occurred and the heart lay horizontally. This is the record of a 69-year-old man, taken several months after his attack. Standard and unipolar extremity leads are what one would expect to find in a normal horizontal heart. There are no signs of infarction in these leads, because the small Q wave is a normal phenomenon with a horizontal heart. However, the precordial leads are typical of anterior infarction.

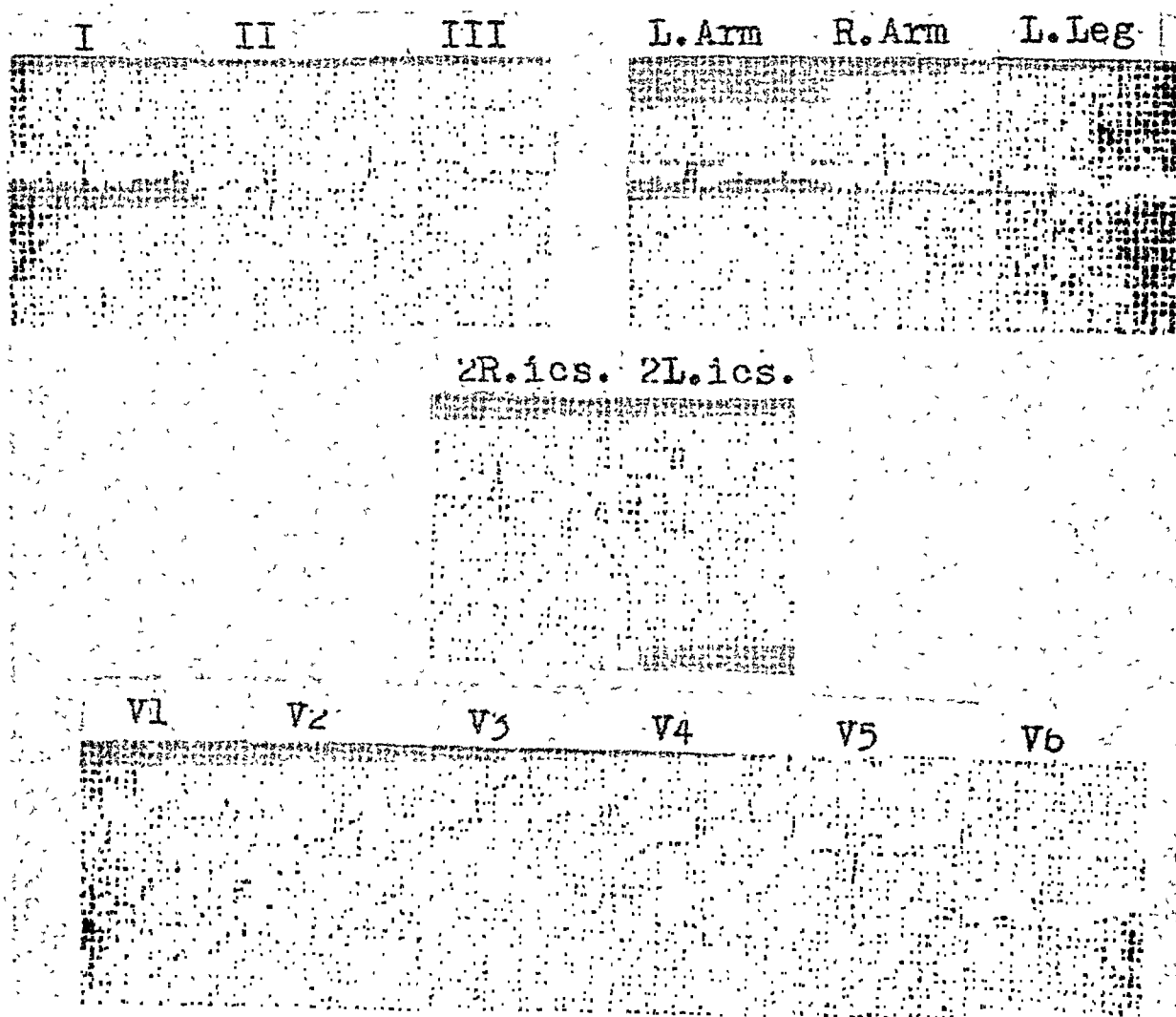


Fig. 10.—Case of anterior infarction with the heart in a vertical position. Y. G., a woman, aged 61 years. For explanation of leads see captions of Figs. 3, 4, and 5.

THE Q WAVE IN CASES OF ANTERIOR INFARCTION WITH THE HEART
LYING VERTICALLY

Fig. 10 is the record of a 61-year-old woman who had an acute myocardial infarction several months before the record illustrated was taken. Precordial and chest leads indicate that the patient was suffering from an anterior infarction, although the standard and unipolar extremity leads are typical of posterior infarction. In spite of the fact that a small Q_1 wave is present, the left arm lead begins with an upstroke. It might be argued in this case that the anterior infarct had also extended to the diaphragmatic surface of the left ventricle to produce the patterns in Leads II and III; nevertheless the fact remains that the patterns of anterior infarction were not projected to the left arm lead because of the vertical position of the heart. Although this combination of extremity lead

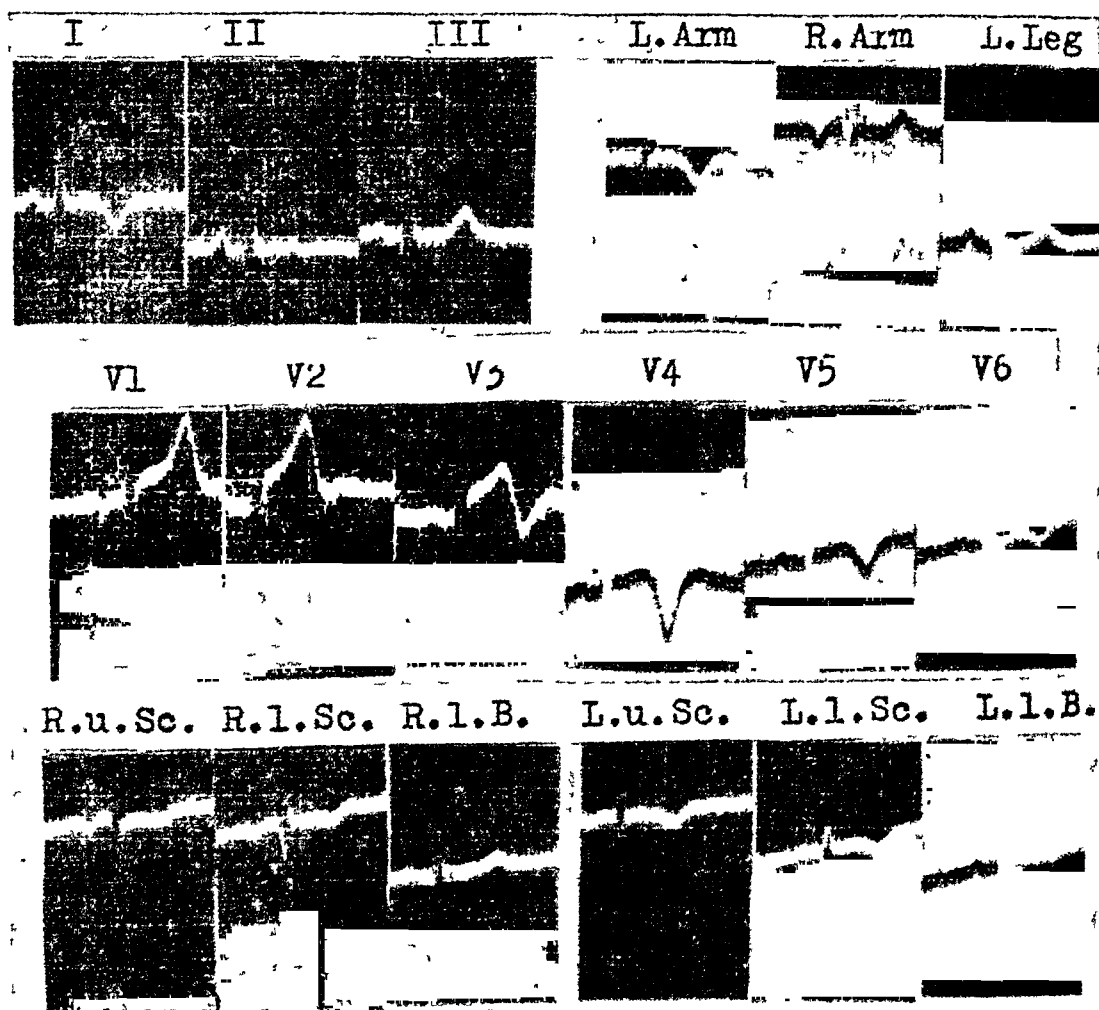


Fig. 11.—A case of anterior infarction with the heart in a vertical position. A. S., a man, 61 years of age. For explanation of leads see captions of Figs. 3, 4, and 5.

and precordial lead patterns is not common, there were five such cases in the series. Fig. 11 is the record of another case of anterior infarction when the heart lay vertically. This was a 61-year-old man who had an acute attack a week prior to the time the record was taken. Standard leads show a typical coved T_1 wave without a Q_1 deflection; whereas in Leads II and III, the typical pattern found in a vertical heart is present: namely, a small Q wave, a high R wave, and an upright T deflection. Study of the precordial leads shows the elevation of the RS-T complex in Leads V_2 and V_3 , without Q waves. In the precordial Leads V_2 and V_6 , small Q waves appear with the elevated RS-T complex. These Q waves, however, are no deeper than the Q waves of

the left leg lead and the unipolar leads from the lower back. Careful exploration of the surface of the body in this patient disclosed no region which had deep Q waves in association with an elevated RS-T complex. The deep Q wave in the unipolar lead from the angle of the right scapula (*R.L.Sc.*) is what one ordinarily finds in a vertical heart.

THE Q WAVE IN CASES OF POSTERIOR INFARCTION WITH THE HEART LYING VERTICALLY.

In a normal or hypertrophied vertical heart, the left ventricle ordinarily faces the left leg lead, and Q waves occur in this lead and in Leads II and III. Furthermore, the T waves in such cases may also point downward in the absence of myocardial infarction. However, elevation of the RS-T segment will not be noted unless infarction has occurred. Fig. 12 illustrates a case of posterior infarction when the heart was more or less vertical. This is the record of a 59-year-old man taken four days after myocardial infarction. Although the left leg lead and Leads II and III have high R waves, there is a high R wave also in the left arm lead and in Lead I, a fact not ordinarily encountered in a vertical heart. Marked elevation of the RS-T segment in the left leg lead and Leads II and III, and marked depression of the RS-T segment of the left arm lead, Lead I, and of the RS-T segments of precordial Leads V_3 and V_4 occur. Precordial Leads V_5 and V_6 have small Q waves, high R deflections, and upright T waves, indicating that the electrodes at these points are facing the left side of the septum and a portion of the normal epicardial surface of the left ventricle.

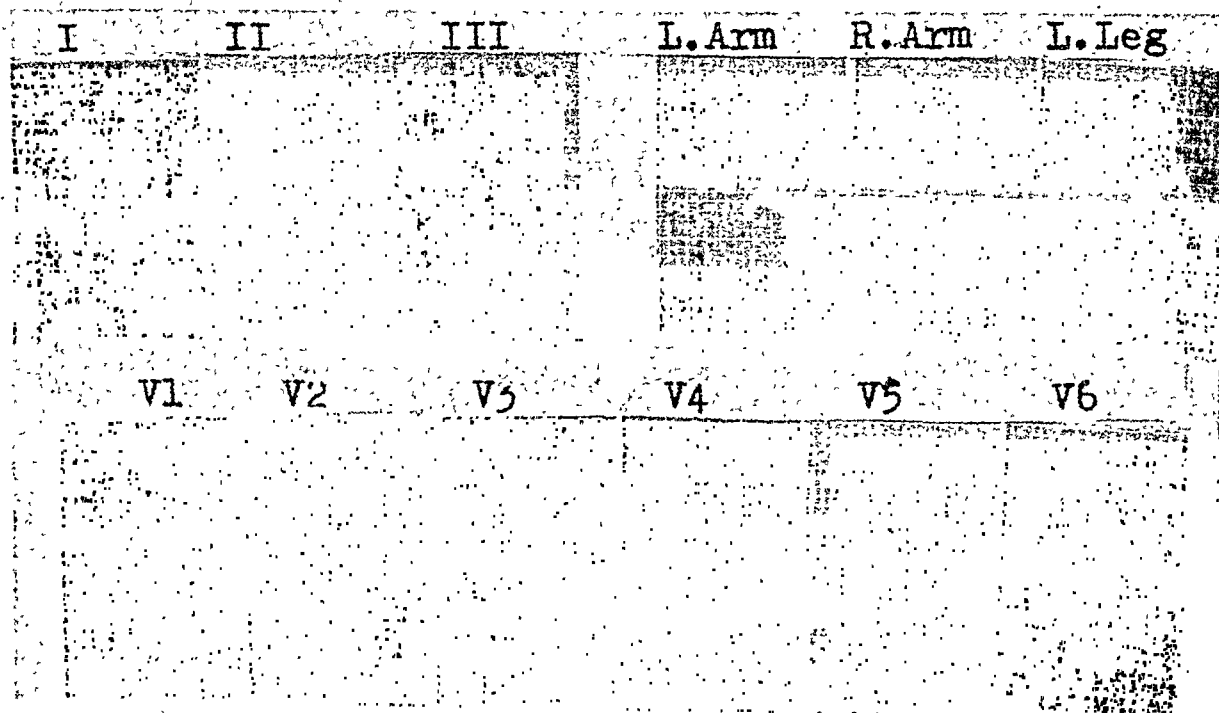


Fig. 12.—A case of posterior infarction with the heart in a vertical position. J. W., a man, aged 59 years.

THE Q WAVE IN CASES OF POSTERIOR INFARCTION WITH THE HEART LYING HORIZONTALLY

Fig. 13 illustrates a case where the peculiarities in the position of the heart produced an unusual distribution of potentials. This is the record of a 62-year-old white man who had been admitted to the hospital for an attack of infarction two days prior to the time the record was taken. The standard and

unipolar extremity leads suggest anterior infarction with the heart in a horizontal position (a Q wave in the left arm lead and an RS deflection in the left leg lead).

Precordial leads are unusual in that the depression of the RS-T segment in leads V_2 , V_3 , and V_4 indicates that the site of the infarct was certainly not on the anterior or medial surface of the left ventricle. The normal configuration of precordial Lead V_6 also indicates that the left lateral wall of the left ventricle was normal, so one must assume that the infarct lay on the posterior wall of the left ventricle but was transmitted to the left arm lead, because of the horizontal position of the heart. Such a record is most unusual. A more usual type of pattern in posterior infarction with a horizontal heart is seen in Fig. 14. This is the record of a 58-year-old man who had suffered an acute

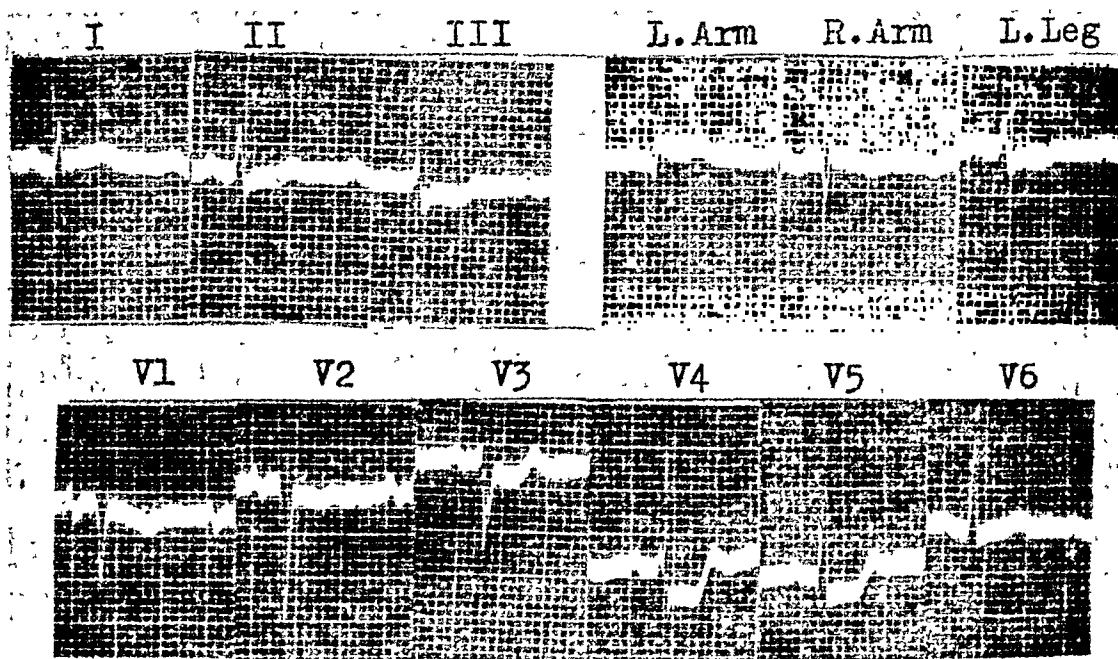


Fig. 13.—A case of posterior infarction, with the heart in a horizontal position. B. V. D., a man, aged 62 years.

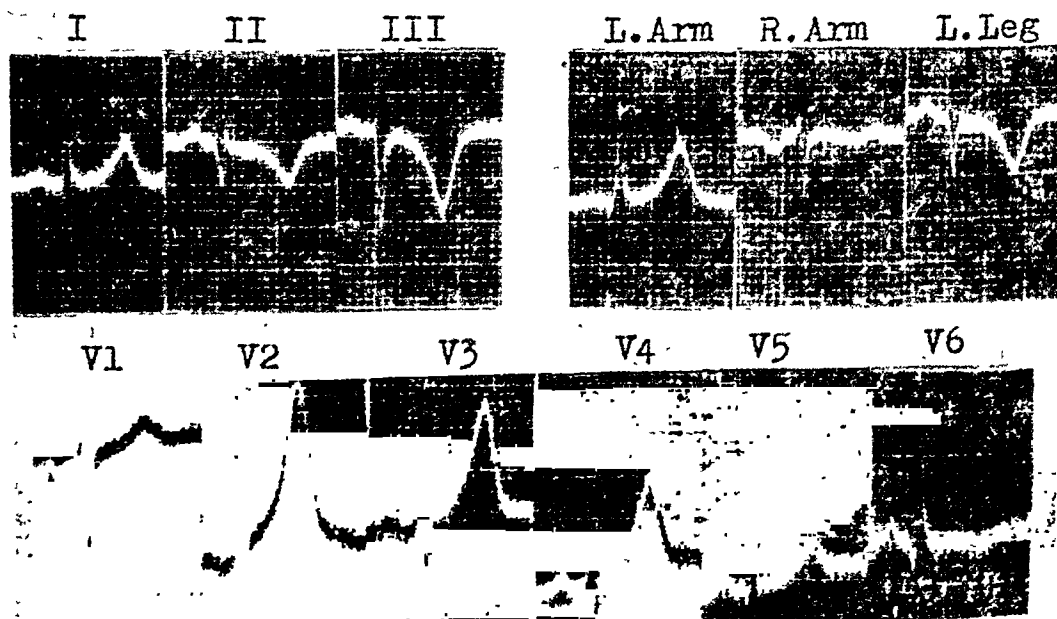


Fig. 14.—A case of posterior infarction with the heart in a horizontal position. L. K., a man, aged 58 years.

attack of infarction about three weeks before this record was taken. The high R wave with a very small Q wave in the left arm lead indicates that the heart is lying horizontally, as does the similarity between the pattern in the left arm lead and precordial Lead V_5 . The left leg lead and Leads II and III show a deep Q deflection with coved T waves. If the position of the heart were typically horizontal, the left leg lead would face the right ventricle and therefore no Q waves would be present. The Q wave in the left leg lead can therefore be explained by the fact that the apex of the heart has been pushed forward, allowing the left leg lead to face the left ventricle. Further evidence for this is the pattern in the right arm lead, which is similar to leads from the right upper chest, and the similarity between the abdominal wall potentials (not shown) and the left leg lead.

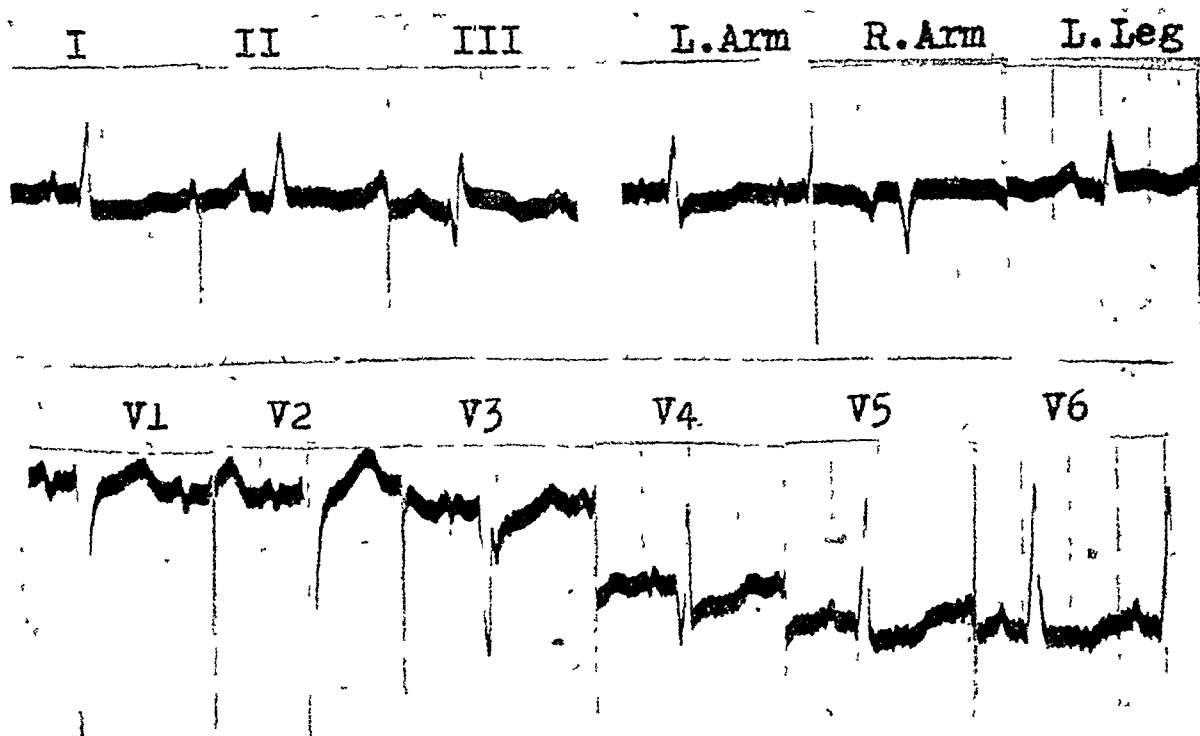


Fig. 15.—A case of multiple infarctions E. M., a man, aged 49 years.

THE Q WAVE IN CASES OF COMBINED ANTERIOR AND POSTERIOR WALL INFARCTION

Fig. 15 is the record of a 49-year-old man who entered the hospital because of an acute attack of myocardial infarction two days before the record was taken. There was a history of a previous attack several years earlier. The elevation of RS-T segment in the left leg leads and Leads II and III, and its depression in the left arm lead and Lead I, suggest the presence of an acute posterior infarction. Q waves are also present in the left leg lead and Leads II and III, but they are small. The absence of the Q wave in the left arm lead is also usual in posterior infarction. Study of the precordial leads show the marked RS-T depressions in Leads V_2 , V_3 , V_4 , V_5 , and V_6 which are typical of an acute posterior infarction, but the deep Q deflection in Lead V_4 suggests the presence of an old anterior infarct. The Q wave of Lead V_4 was not transmitted to the left arm lead, however, because of the position of the heart.

THE Q WAVE IN CASES OF BUNDLE BRANCH BLOCK

Right Bundle Branch Block.—In right bundle branch block the left side of the septum is the first portion of the ventricle to be activated. Therefore unipolar leads facing the left ventricle will record a Q wave. When the heart is

horizontal the left arm lead and Lead I will have a Q wave, and when the heart is vertical the left leg lead and Leads II and III will record a Q wave.⁷ Infarction of the left ventricle, complicated by right bundle branch block, does not prevent the Q waves from appearing.¹²

Left Bundle Branch Block.—In left bundle branch block, the right side of the septum is activated first. A unipolar lead overlying, or facing, the left ventricle, therefore, will record an initial upward deflection.⁷ When the heart is horizontal, the left arm faces the left ventricle and the left arm lead and Lead I begin with an upstroke. When the heart is vertical the left leg lead and Leads II and III begin with an upstroke, and the left arm lead and Lead I may be entirely downward.^{7, 12} Such a pattern is, however, quite rare. Infarction of the left ventricle complicated by left bundle branch block is characterized by the disappearance of the Q waves, even from unipolar leads overlying the infarct. The cause of this is that the left side of the septum is positive at the onset of the QRS deflection. It has been stated that in such cases, if the septum is also infarcted, a Q wave may be seen even with the left bundle branch block.¹² I have had no experience with cases of this type. In a recent paper, cases of left bundle branch block with a Q₁ were discussed.¹⁷ Although no records were presented, I reviewed the cases in the literature cited in this paper. I do not think that such records represent left bundle branch block. Further discussion of this problem is presented elsewhere.⁷

DISCUSSION

The presence or absence of Q waves would be a matter of academic importance were it not for the fact that Q waves are an important sign of myocardial infarction and that, after the infarct has healed, they may constitute the only sign that infarction had occurred. Statistical surveys of the incidence of the various Q-wave combinations have not been too successful in providing a means of differentiating a normal from an abnormal Q wave in the standard leads. One of the reasons for this is the fact that the Q deflection in the standard leads may be the result of a variety of combinations of potential. Another reason for this is that the Q deflection is essentially a normal wave. Basically the Q wave can only be considered abnormal if it constitutes the main ventricular deflection in a unipolar lead overlying the epicardial surface of the left ventricle. In a case of anterior infarction the left arm lead usually faces the infarct and consequently a deep Q wave and coved T deflection will appear in the left arm lead and Lead I. However, it is known that, in a horizontal heart, a Q wave may occur (with a high R deflection and with a downward T wave); and, when the heart is vertical, the left arm lead may consist of a QS deflection and a downward T wave (Fig. 16).

We therefore attempted to determine statistically if the Q wave in the left arm Lead due to infarction might have different characteristics than the Q deflection of the vertical or horizontal heart. The Q-LA deflection was studied in fifty cases of anterior infarction and in one hundred cases where the heart was either normal or hypertrophied. In these cases the duration of the Q wave was measured in the manner previously described. The proportion between the depth of the Q wave to the amplitude of the entire QRS complex was also determined. The depth of the Q or S wave was measured from the lower edge of the string shadow at the end of the P-R interval to the apex of the Q wave. The height of the R deflection was measured from the upper edge of the string shadow at the end of the P-R interval to the apex of the R wave. The values of R and Q (or S, if an S wave occurred and was deeper than the

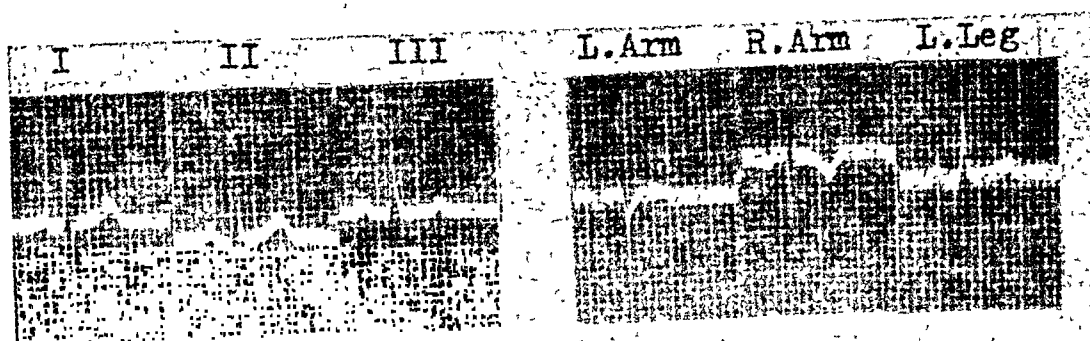
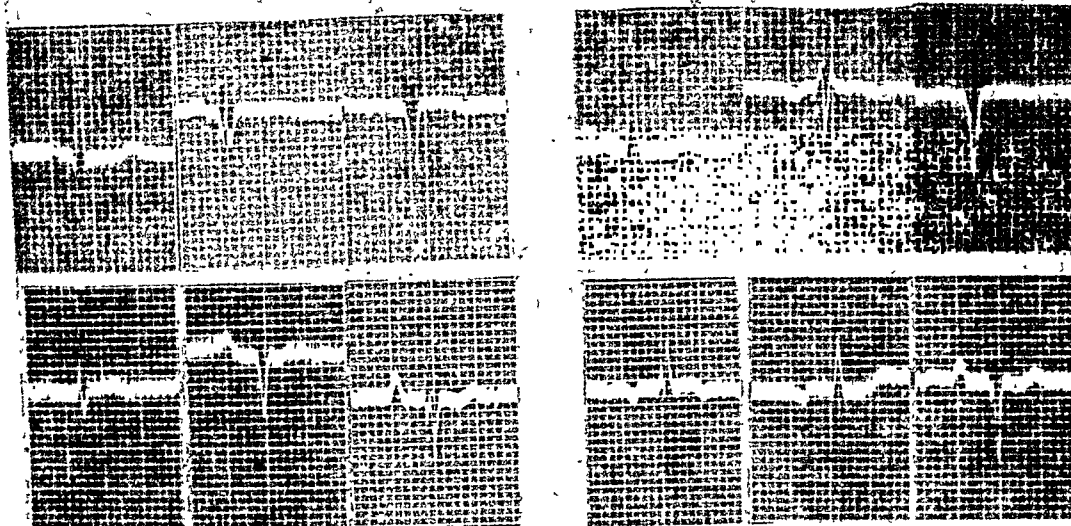


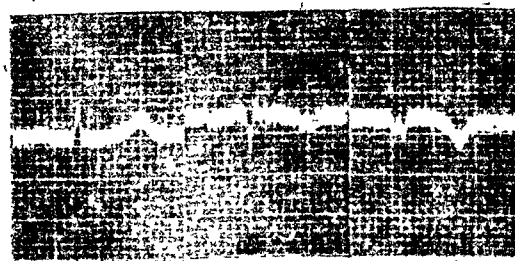
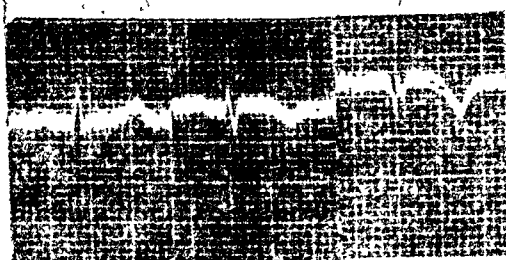
Fig. 16.



a.

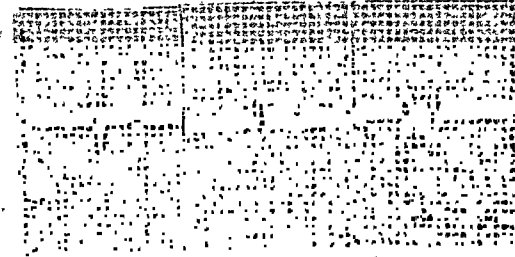
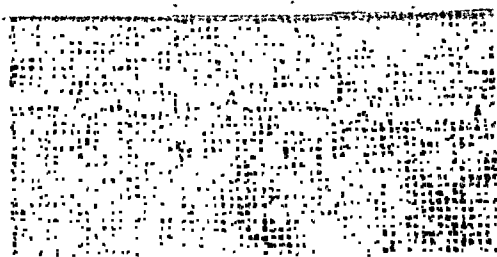
Fig. 17.

b.



a.

Fig. 18.



b.

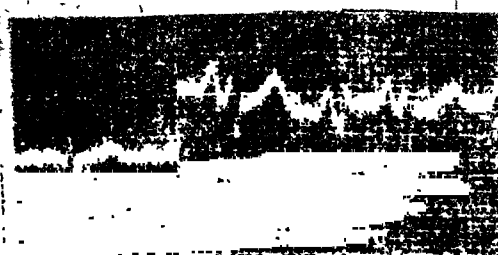


Fig. 19.

Fig. 16.—A normal vertical heart. M. B., a man aged 29 years. Note the QS deflection in the left arm lead.

Fig. 17.—Two cases showing QS deflections in the left leg lead. *a*, A case of old posterior infarction. I. G., a man, aged 85 years. *b*, A case of bilateral pulmonary tuberculosis. A. B., a man, aged 27 years.

Fig. 18.—Two cases showing a W-shaped QRS complex in the left leg lead. *a*, A case of posterior infarction. A. D., a man, aged 53 years. *b*, A case of chronic asthma and emphysema. J. M., a man, aged 57 years.

Fig. 19.—A case showing a Q wave and downward T deflection in the left arm lead in the absence of infarction. S. K., a man, aged 61 years. Chronic asthma and emphysema. The QR deflection in the right arm lead indicates that the apex of the heart has been displaced backward. Note the similarity of the left arm and right arm leads, and the negative P deflection of the left arm lead,

Q wave) were then added to get the amplitude of the QRS complex. The relation of the depth of the Q wave to the amplitude of the QRS complex was expressed as a percentage.

The characteristics of the T wave and RS-T segment were noted. In fifty cases of anterior infarction, eighteen had a Q wave with a duration of 0.04 second or more, and an amplitude of 30 per cent or more of the entire QRS complex. Five cases had a QS deflection. However, in twenty-seven cases, Q-LA had a duration of less than 0.04 second and an amplitude of less than 30 per cent of the QRS complex. Five of the series of one hundred normal cases had a Q wave with a duration of 0.04 second. In the remaining, the duration of the Q-LA interval was less than 0.04 second. In seven cases, a QS wave was noted in the absence of myocardial infarction (Figs. 6 and 16).

We can therefore conclude that a wide, deep Q wave in the left arm lead, with a depth of 0.04 second or more, comprising 30 per cent or more of the entire QRS complex (excluding a QS deflection), in association with a coved T wave is a presumptive sign of infarction, although this pattern may be present in the absence of infarction, and infarction may be present in the absence of this pattern. In such cases without infarction, the P wave is likely to be very negative in the left arm lead (Fig. 19). Inasmuch as a diagnosis of anterior infarction can be made more advantageously with unipolar precordial leads, the use of the characteristics of the Q wave in the left arm lead as a sign of infarction is not to be recommended. However, in the case of posterior infarction of the left ventricle, the infarct usually overlies the diaphragm, and it therefore is difficult to obtain unipolar leads overlying the infarct, unless esophageal leads are used. The left leg lead, however, ordinarily faces the infarct, and has the characteristic deep Q wave and elevated RS-T segment in cases of posterior infarction. A Q wave in the left leg lead is, as we have pointed out, very often a normal phenomenon. For this reason, we analyzed fifty cases of posterior infarction and one hundred cases of normal and hypertrophied hearts with a Q wave in the left leg lead in a manner similar to that used in cases of anterior infarction. The results were significant. We found thirty of the fifty cases of posterior infarction with a Q wave whose amplitude equaled or exceeded 40 per cent of the entire QRS complex. In these cases, the T wave was coved in all but three. These latter were instances of old healed posterior infarction. In all but one of the thirty cases, the duration of Q was 0.04 second or more. Six cases had a QS deflection, with a wide Q wave. Three of these cases had an upward T wave (Fig. 17,a). Nine cases had a small W-shaped QRS deflection with a coved T (Fig. 18,a). In most of these it was difficult to measure the width of the Q wave. Five cases had a small Q wave whose amplitude was less than 40 per cent of the entire QRS complex. In one case, the width of the Q wave was also less than 0.04 second. All five cases, however, had elevation of the RS-T segment and coving of the T wave. Of the one hundred normal records, only two had a Q wave which was 40 per cent or more of the entire QRS deflection. The width of the Q wave in these two cases was less than 0.04 second. Furthermore, the width of the Q wave in all but three of the one hundred cases was within 0.04 second. There were four cases with a QS deflection (Fig. 17,b) and five cases with a small W-shaped QRS complex (Fig. 18,b).

It is therefore concluded that, when the Q wave in the left leg lead has a duration of 0.04 second or more, and has an amplitude of 40 per cent or more of the entire QRS complex (and is not W-shaped or does not consist of a QS deflection), such a record indicates posterior infarction. In most of these cases the

RS-T segment will be elevated or the T wave will be coved, but, after healing of the infarct has taken place, the T deflection may become upright.

CONCLUSIONS

In cases of normal conduction or right bundle branch block, the Q wave, as recorded in unipolar leads, is due to the fact that the left side of the interventricular septum is activated before the right side.

The characteristics and depth of the Q deflection varies with the position of the electrode. If the electrode tends to face the left ventricular cavity, the entire QRS complex may consist of a QS deflection. The duration of the Q wave, therefore, will be 0.04 second or more. If the electrode faces the epicardial surface of the left ventricle, the Q deflection is small in comparison with the tall R wave which follows (less than 30 per cent of the entire QRS complex) and its width is less than 0.04 second.

There are other mechanisms by which a Q wave may appear. If a lead which faces the right ventricle and ordinarily records an RS deflection is placed so that it tends to lie on the same plane as the interventricular septum, the initial activity in the septum, running at right angles to the plane of the septum, will be without effect on the electrode, and the initial upward deflection may not be recorded, so that the QRS appears as a QS deflection.

In infarction of the left ventricle involving the greater thickness of a portion of the wall, an electrode overlying, or facing, the infarct will record not only the initial negativity of the left side of the septum but, because the infarcted muscle has lost its electrical activity, the infarct acts like a window in the ventricular wall and the remaining portion of the QRS complex is negative, which is the potential of the ventricular cavity during the inscription of the QRS complex.

Since Q is an initial downward deflection, its presence in unipolar extremity leads has a different meaning than a Q wave in the standard leads. However, certain relations between standard and unipolar leads exist in that Leads II and III tend to resemble the left leg lead, and Lead I tends to resemble the left arm lead.

Variations in the location of the Q deflection in the extremity leads depends on the position of the heart. If the heart lies horizontally, the left arm lead faces the epicardial surface of the left ventricle and a Q wave with a tall R deflection will usually be seen in the left arm lead and Lead I. If the heart lies vertically, the left leg lead usually faces the epicardial surface of the left ventricle and a Q wave and high R deflection appear in the left leg lead and Leads II and III. However, if the apex of such a heart is displaced backward, the left leg lead faces the right ventricle and the Q waves disappear. If a vertical heart has marked clockwise rotation around its long axis, small Q waves may appear in precordial leads to the right of the sternum.

With infarction of the ventricles, Q waves will not appear if the infarct involves the right ventricle or an area near the plane of the interventricular septum.

With infarction of the anteriorlateral surface of the left ventricle the RS-T segment elevation may be observed with small Q waves which are due (as in a normal heart) to the activation of the left side of the septum, or with very deep QS deflections which are due to the fact that the greater thickness of a portion of the muscle wall has been infarcted.

If the entire surface of the left ventricle is not infarcted, regions will be found overlying normal muscle in which a small normal Q wave may be

recorded with a high R deflection and upright or high T wave (or with a depression of the RS-T segment).

Although the patterns of anterior infarction are usually transmitted to the left arm lead and Lead I, and the patterns of posterior infarction are usually transmitted to the left leg lead and Leads II and III, variations in the distribution of the patterns may occur because of the position of the heart. Thus, with anterior infarction, if the heart be vertical, Leads II and III may record the characteristic Q wave and elevated RS-T segment. Similarly, with posterior infarction, if the heart be horizontal, Lead I may record the Q wave and elevated RS-T segment.

The distribution of the Q wave in cases of right bundle branch block is similar to that in the normal heart. Right bundle branch block, complicating infarction of the left ventricle, does not result in the disappearance of the characteristic Q waves.

In cases of left bundle branch block, the initial deflection in leads facing the left ventricle is upward; consequently, left bundle branch block complicating infarction of the left ventricle results in the disappearance of Q waves.

In left bundle branch block without infarction, the heart usually lies horizontally, and the left arm lead and Lead I do not record a Q wave, although a Q deflection may be present in the left leg lead and Lead III.

Statistical study of the Q waves of the unipolar extremity leads in normal cases and after infarction allows certain conclusions to be drawn: In the left arm lead, if the Q deflection comprises more than 30 per cent of the entire QRS complex, has a width of 0.04 second or more, and is associated with a downward T wave, such a pattern is usually due to anterior infarction, although such a pattern may occasionally be seen in a vertical heart with marked clockwise rotation and displacement of the apex of the heart backward (Fig. 19). If the pattern is due to a vertical heart, the P wave is usually deeply negative, a finding which does not ordinarily occur with infarction. Furthermore, study of the precordial leads in such cases will establish the presence or absence of an infarct.

In the left leg lead, if the Q deflection has an amplitude of 40 per cent or more of the entire QRS complex, and it has a duration of 0.04 second or more and is associated with a downward T deflection, such a pattern is usually due to posterior infarction. However, similar records, especially if the QRS complex consists of a QS deflection or of a small W-shaped complex, are occasionally met with in cases without infarction. Such records ordinarily have very large P waves and the precordial leads in such cases give evidence usually of enlargement of the right ventricle.

The author wishes to express his appreciation to Dr. Louis Leiter, Chief of the Medical Division, Montefiore Hospital, to Dr. Sidney P. Schwartz, Cardiographer, Montefiore Hospital, and to Dr. Leander H. Shearer, Director of the Department of Medicine, Lincoln Hospital, for their generous cooperation.

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ADDENDUM

Myers and Oren, in a recent paper ("The Use of the Augmented Left Leg Lead in the Differentiation of the Normal From the Abnormal Q Wave in Standard Lead III," *AM. HEART J.* 29: 708, 1945), studied the relation between the Q wave in the left leg lead and the R wave in the left leg lead in cases of myocardial infarction, instead of determining the relation between the Q wave and the entire QRS complex, as we did. They found that, when Q_{LL} had 25 per cent or more the amplitude of R_{LL} , a diagnosis of posterior infarction could be suspected from this alone.

We reinvestigated our measurements in the left leg lead in cases of posterior infarction, using the relation between Q and R instead of between Q and QRS. We found that, when Q_{LL} had 60 per cent or more the amplitude of R_{LL} and was 0.04 second or more wide, myocardial infarction was usually present unless the left leg lead showed a QS pattern or a W-shaped QRS complex.

DETERMINATION OF CIRCULATION TIME; UNSUITABILITY OF PAPAVERINE

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NUMEROUS methods are available for determining the velocity of blood flow. Subjective methods for estimating the circulation time have the important disadvantage that the cooperation of the patient is required. Objective methods on the other hand require, in some instances, rather special apparatus. With both methods the substance introduced into the blood stream may prove toxic.

Sodium dehydrocholate (Decholin) has been used for measuring the circulation time. In view of the fact that this method depends on a subjective re-

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sponse, the patient's signalling the development of a bitter taste in the mouth, and because occasional unpleasant reactions have occurred (Leys¹), we have sought an easy objective method.

Papaverine hydrochloride was used by Elek and Solarz,² who reported successful determination of circulation time by injecting this drug into an ante-cubital vein and noting the end point, described as a sudden deep inspiration, with a sigh or exclamation, commonly followed by flushing of the face, mild dizziness, and tachypnea. No other reports on this method appear in the literature.

We have used the method described by the authors,² with one exception: the dose of papaverine hydrochloride, 40 mg., was administered in solution in 1.6 instead of 1.25 cubic centimeters. The method was unsatisfactory in our hands. The results are described.

RESULTS

Fifty patients, hospitalized for various disorders and aged 20 to 80 years, were used in this study. In thirteen patients (26 per cent) the end point was good—a deep inspiration occurred. In seventeen (34 per cent) the reaction was not satisfactory—the end point was very difficult to determine. In twenty (40 per cent) no reading at all could be obtained.

Duplicate readings were made in those cases in which a sharp end point was observed. The results of the tests with satisfactory end points are given in Table I.

TABLE I. DETERMINATION OF CIRCULATION TIME WITH PAPAVERINE

DIAGNOSIS	FIRST READING (SEC.)	SECOND READING (SEC.)
Thyrototoxicosis	19	18½
Hemophilia	19	18
Hemolytic anemia	15	20
Pernicious anemia	23	21
Pneumonia	17½	18
Bronchiectasis	18½	23½
Pleural effusion	20	20
Peripheral neuritis	16	21
Peripheral neuritis	20	21½
Hypertensive heart failure	18½	17
Mitral stenosis with congestive failure	19	15
Dysentery	24	24½
Abdominal tumor	23	21

COMMENT

The injection of papaverine hydrochloride to estimate the circulation time has not proved successful in our hands. The following difficulties were encountered.

1. In a major proportion of patients no satisfactory end point was obtained.
2. In patients in whom sharp end points were obtained, duplicate determinations differed by as much as 5 seconds.
3. No satisfactory differences in circulation time occurred in patients with thyrototoxicosis, congestive heart failure, or anemia or in normal subjects which were of any clinical value.

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ELECTROCARDIOGRAPHIC FEATURES OF MYOCARDIAL INFARCTION AS AFFECTED BY INVOLVEMENT OF THE SEPTUM AND BY COMPLETE AND INCOMPLETE TRANSMURAL INVOLVEMENT

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IT HAS seemed to the authors that many of the current theories as to the causation of abnormalities of the S-T junction and T wave and the appearance of the Q and the Q-S deflections after myocardial infarction are in need of testing against the findings in human autopsy material. It was decided, therefore, to review a series of cases, correlating the exact situation and extent of the infarcted areas with the electrocardiographic findings. Leads I, II, III, and IVF were recorded in this series.

The usual pathologic descriptions, as found in autopsy reports, were insufficiently detailed for this purpose and so it was thought advisable to confine the study to a group of hearts that could be re-examined because they had been preserved in the Pathological Department of The New York Hospital. It was possible to obtain eleven hearts of patients who had died of a recent infarction and one with an old healed infarct. All but one of these patients had died after a severe, acute attack due to coronary thrombosis which occurred within three to fifteen days after the initial symptoms developed. The one with a healed infarct died of metastatic carcinoma two years after an attack of coronary thrombosis. These hearts were examined with the assistance and usually with the actual personal cooperation of Dr. William Dock. When he was not available, other members of the Pathological Department were consulted. The exact location of the infarct in relation to posterior, lateral, and anterior walls and septum was noted and it was observed whether or not the epicardial or endocardial muscle layers were affected throughout the area of the infarct. The pathologic findings in these cases are summarized in Table I.

TABLE I. DISTRIBUTION OF NECROSIS AND SCARRING

PORTION OF HEART	CASE											
	1	2	3	4	5	6	7	8	9	10	11	12
Subepicardial	+	sc
Anterior wall	+ sc	+	+	+
Subendocardial	+
Anterior septum	+ sc	+	.	+	+	sc	.	.	sc	.	sc	.
Subepicardial	+	.	+	+	sl
Posterior wall	.	+	sc	.	.	.	sc	+	+ sc	+	+	+
Subendocardial	+	+	+	+	+
Posterior septum	+	+	+	+	sl
Lateral wall	.	.	.	sl	.	+	sc	.	.	+	+	.

+ indicates necrosis.

sc indicates scarring.

sl indicates a small area of necrosis only.

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CLINICAL AND ANATOMIC FINDINGS

CASE 1.—On the morning of the day of admission, the patient had a severe coughing spell, collapsed, and became unconscious. On admission, the heart sounds were faint, almost inaudible. The patient died on the day after admission after gradually increasing respiratory difficulty and weakening pulse. The heart was not enlarged. The right coronary artery was thrombosed, and the anterior descending branch was also thrombosed; the circumflex branch was patent. There was extensive old scarring in the anterior part of septum and the adjacent anterior wall and apex. A new infarct was noted in the median portion of the anterior wall adjacent to the old scar, affecting the entire thickness of the muscle.

CASE 2.—The patient had had heart disease for five years. Four years previously, he was said to have had myocardial infarction. He was known to have had blood pressure measurement of 220/130, fifteen months before the present illness. The patient was admitted in heart failure of one month's duration, with auricular fibrillation with an apical rate of 126 per minute. On the third hospital day, he developed severe precordial pain radiating into both arms. The blood pressure measurements became difficult to obtain; the pulse was almost imperceptible; and the respirations were 48 per minute. The patient died five days later after progressively increasing pulmonary congestion. The heart was much enlarged. The right coronary artery was patent; the anterior descending branch was thrombosed; the circumflex branch appeared patent; and a small branch in the lateral wall was thrombosed. There was a large, recent infarct of the anterior wall and septum, reaching the endocardium in both areas, extending to posterolateral wall through the apex. The pericardium and endocardium in the posterior wall, and the epicardium were not involved.

CASE 3.—Three days before admission, the patient experienced severe pain in the chest radiating to the right shoulder and arm; nausea and vomiting. He was very short of breath. The cough and shortness of breath grew worse. He entered the hospital on the third day, at which time he was cyanotic and orthopneic. The heart sounds were faint, and the lungs showed numerous moist râles; the ankles showed 1 plus edema. He continued about the same for five days and then died suddenly. The heart was slightly enlarged. The right coronary artery appeared to be narrowed at the orifice by syphilitic aortitis; otherwise it was patent. The anterior descending branch was narrowed and a large subsidiary branch of this was also narrowed. The circumflex branch was thrombosed; a branch of the circumflex artery appeared narrowed. There were old scars in the posterior wall. A large infarct was found in the anterior wall, extending to the lateral wall but neither the endocardial nor the pericardial surfaces were involved. The infarct did not extend into the septum.

CASE 4.—The day before admission, the patient experienced a severe attack of epigastric pain, radiating laterally around the lower ribs and to the arms. By evening these pains were almost continuous. He was awakened at 1:00 A.M., on the day of admission, by an especially severe and prolonged pain. On the sixth day, the temperature was 39.6° C., the pulse was 90 per minute, the respirations were 20, and the blood pressure measured 130/85. On the second day after admission, he developed persistent, aching, precordial pain and a pericardial rub was heard. This continued for only two or three days, but the pain subsided more slowly. He seemed to be progressing in a satisfactory manner when suddenly, on the twentieth day after the infarct, he developed an attack of severe dyspnea, with a markedly irregular pulse, which became very fast. Shortly thereafter he died. The heart was not enlarged. The right coronary artery was patent. The anterior descending branch was thrombosed; the circumflex branch was open. There was a recent infarct in the anterior portion of the septum on the endocardial surface only, extending into the anterior wall of the left ventricle as far as the lateral wall. The process was entirely subendocardial. The epicardium was involved only laterally and, there, not extensively.

CASE 5.—Two days before admission, the patient had intermittent attacks of precordial pain which recurred on the day preceding admission. He entered the hospital with a temperature of 38.4° C.; pulse rate 100 per minute, and respirations 20. The blood pressure measured 165/100. The leucocytes were 32,000 per cubic millimeter. There were minimal râles in the bases of the lungs. His course was very satisfactory for nine days, when he suddenly became pale and very short of breath; he died in a short time. The heart was small. The right coronary artery and circumflex branch of the left were patent. The left descending branch was open but the septal branch was thrombosed. An infarct of the anterior portion of the septum was observed extending to the apex, but not reaching the epicardial surface. It was subendocardial in the left ventricle and also to a lesser extent in the right ventricle. No involvement of the anterior wall of the left ventricle or of the posterior portion of the septum was noted.

CASE 6.—The day before admission, the patient had severe pain beneath the sternum and over the precordium, lasting until the time of admission. The temperature ranged between 37.8° C. and 39° C.; the pulse rate was 92 per minute; and the blood pressure measured 132/88 (the systolic value had been 260 four years previously). The white blood cells were 17,000 per cubic millimeter. The course was uneventful for eight days but, on the ninth day after admission, there was increasing respiratory distress. The patient died on the following day, eleven days after the attack. The heart was slightly enlarged. The right coronary artery showed a recent thrombus; the anterior descending branch was patent and the circumflex branch was the site of a recent thrombus. Old scars were seen in the anterior portion of the septum, extending to the epicardial surface, but the endocardium was not reached. There was a recent extensive lateral infarct, extending from 2 cm. lateral to the anterior margin of the septum, around to the posterior wall. The posterior part of the septum was not involved. The infarct really lay more posteriorly than anteriorly, definitely posterolateral.

CASE 7.—The patient had experienced an attack of coronary thrombosis two years before admission. The symptoms were severe precordial pain, shortness of breath, orthopnea, weakness, and loss of appetite. Rest in bed had been enjoined for six weeks. The patient was admitted because of disability from carcinoma of the ovary with metastasis. The electrocardiogram was taken on the day after admission, about three months before death. The heart was not enlarged. The coronary artery appeared patent, and the anterior descending branch was narrowed. The circumflex branch was narrowed with one area of closure. The lateral wall, near the apex, was scarred, and the apex was involved in its posterior portion. The septum was not involved.

CASE 8.—The patient was known to have had hypertension for four years before admission. A week preceding admission, gradually increasing weakness and shortness of breath occurred when at rest. Three days before admission, he had slight precordial oppression which lasted several hours. He was admitted with pulse barely perceptible. The temperature was 36.8° C. The blood pressure measured 80/60. The heart sounds were weak and the lungs contained numerous moist râles. The temperature was persistently high, and the patient died with increasing shortness of breath and pulmonary congestion on the sixth day after admission. It is noteworthy that this patient did not have a well-defined date of onset.

The heart was not enlarged. The right coronary artery was patent, and the anterior descending branch was open. The circumflex branch was narrowed to 1 mm. in diameter and a superficial descending branch on the posterior aspect was thrombosed. There was an infarct in the posterior wall, involving the epicardial and endocardial surfaces, but the septum was spared. The necrotic area was 3 by 3 centimeters.

CASE 9.—For three nights before admission, the patient had felt precordial pain while in bed. On the night before admission, the pain was unusually severe and was associated with nausea and vomiting. The temperature on admission was 37.4° C., and the pulse rate was 130 per minute. The blood pressure measured 106/74. The maximum temperature during hospitalization was 38.2° C. The patient developed increasing signs of cardiac failure but left the hospital on the seventh day against advice. He died the following night at his home. The heart was much enlarged. One-third of the right coronary artery was occluded. The anterior descending branch was thrombosed. One-half of the circumflex branch was occluded. There was an old infarct of the anterior portion of the septum, with thinning of the apex. There was a fresh infarct involving the endocardium of the posterior wall, but the epicardium and septum were not involved. It would seem that the posterior infarct might have been due to closure of the anterior branch combined with the narrowing of the other blood channels.

CASE 10.—No symptoms referable to the heart had been experienced by this patient who was being treated in the rhino-otolaryngologic clinic by irrigation of the antrum. After returning home from one of these visits, he collapsed and became semicomatose. On admission to the hospital, the heart sounds were almost inaudible, the lungs showed râles at both bases, and the blood pressure was 100/65. The temperature was 38.8° C. The blood pressure gradually fell, and he died on the second day after admission. The heart was somewhat enlarged. There was a thrombus in the right coronary artery; the anterior descending branch showed a recent thrombus. A similar finding was present in the circumflex branch. There were fibrous bands in the anterior portion of the septum. A recent infarct was observed in the posterior wall and the posterior part of the septum, extending to both epicardial and endocardial surfaces.

CASE 11.—The patient was admitted to the hospital with heart failure and hypertension and for eleven days made satisfactory progress under treatment. He then had an attack of severe pain with vomiting, followed by a rise in temperature which went as high as 39.3° C. The blood pressure fell to 110/98. There was an elevated sedimentation rate and a leucocytosis of 19,000 cells per cubic millimeter. The pain subsided and he was making satisfactory progress but died suddenly on the sixth day after the attack. The heart was much enlarged. The right coronary artery showed a recent thrombosis; the left anterior descending branch exhibited an old closure; the circumflex branch was the site of a recent thrombosis. There was old scarring in the anterior wall which did not involve the epicardial layer. A large recent infarct was found in the posterior wall, extending into the septum and into the apex and somewhat laterally, involving both endocardial and epicardial surfaces.

CASE 12.—Two days before admission, the patient experienced an attack of severe excruciating pain in the left side of the chest, extending to the arm. The following day he was able to be up but, on the second day, he had a temperature of 39° C. and felt very weak. He was admitted to the hospital at this time. The blood pressure was 125/75; the pulse rate was 110 per minute; and the respirations were 32. He developed cardiac failure following admission and died on the seventh day. The heart was slightly enlarged. The right coronary artery seemed patent. The anterior descending branch was narrowed; the circumflex branch contained a recent thrombus. There was a large intramural infarct on the posterior wall with lateral extension. Only two small areas, each about 4 by 8 mm., extended to the epicardial surface. The smaller of these reached the endocardium.

ELECTROCARDIOGRAPHIC FINDINGS

Cases 1 and 2 showed areas of infarction involving the anterior wall and the anterior part of the septum. In Case 1 the entire thickness of the anterior wall was necrotic, but in Case 2 the subepicardial fibers were not involved to a depth of 4 millimeters. The electrocardiograms of both these cases showed the typical appearance associated with acute anterior infarction, both in the limb leads and in the precordial lead (Fig. 1,B). The Q_1 and $Q-S_4$ deflections were present in both cases, as well as the usual elevation of the S-T junction in Leads I and IV, with depression in Lead III. It is noteworthy that in Case 2 the subepicardial layers of muscle were not necrotic, because in the records taken after the infarction (Fig. 1,B, C, and D) the precordial lead had lost the R wave (preintrinsic deflection), showing only a large Q-S wave. This feature has been attributed to the effect of a lesion extending entirely through the ventricular wall, yet such a condition was not found in this heart. It is well recognized that the function of muscle is not always indicated by its structural appearance. A damaged portion of heart muscle may give rise to abnormal electrocardiographic features and yet may appear normal on later microscopic examination, provided that the damage has not been too severe or of too long duration. The marked S-T deviation in the early record may indicate a transient phase of damage to these superficial muscle fibers; their ultimate recovery is suggested by the more normal form of T_4 in Fig. 1,D. The regression of the early S-T and T-wave changes was unusually rapid in this case, since it almost disappeared from the limb leads in two days (Fig. 1,C). One might assume that this rapid regression was associated with a recovery of function in the surviving subepicardial layers, but if this were so, it is surprising that the R wave did not reappear in the precordial lead of the later records (Fig. 1,C and D) as experimental observations would have led us to expect with such a recovery. It is of interest also that this heart, in addition to the infarct in the anterior wall, had intramural involvement in the posterior wall, not reaching either the endocardial or epicardial surfaces, and that there was nothing in the electrocardiogram to suggest posterior wall involvement.

There were four cases which might be said to represent incomplete anterior infarcts, as the complete thickness of the wall was not involved (Cases

2, 3, 4, and 5). In Case 3, the infarct was entirely intramural, as it involved the deeper layers of the anterior wall, but it did not reach either the endocardial or epicardial surfaces nor did it extend into the septum. A record before infarction (Fig. 2,C) showed a normal axis of the QRS complex with Q_2 and Q_3 waves. After infarction (Fig. 2,D) the axis of the QRS complex was at the right border of the normal sector, and the Q_3 deflection was absent. The S-T junction in Lead I was +1 mm., and the T wave was upright. The S-T junction in Lead II was -1 mm., and the T wave was inverted. The S-T junction in Lead III was -2 mm., and the T wave was inverted. In Lead IV the QRS, S-T, and T waves showed little change from their previous normal form except in amplitude. The R wave persisted, as might be expected by analogy with experimental results with an anterior infarct not reaching the epicardium, but there was no Q_4 deflection, as would have been expected with such a lesion.² It is of interest that the Q_3 deflection was abolished by an intramural lesion of the anterior wall which did not involve the anterior part of the septum. The appearance of the S-T segment and the T waves in the limb leads was much like that seen after anginal attacks,³ anoxemia,⁴ and exercise tests.⁵ Considering the four-lead electrocardiogram, one could not definitely say that it indicated an anterior infarction.

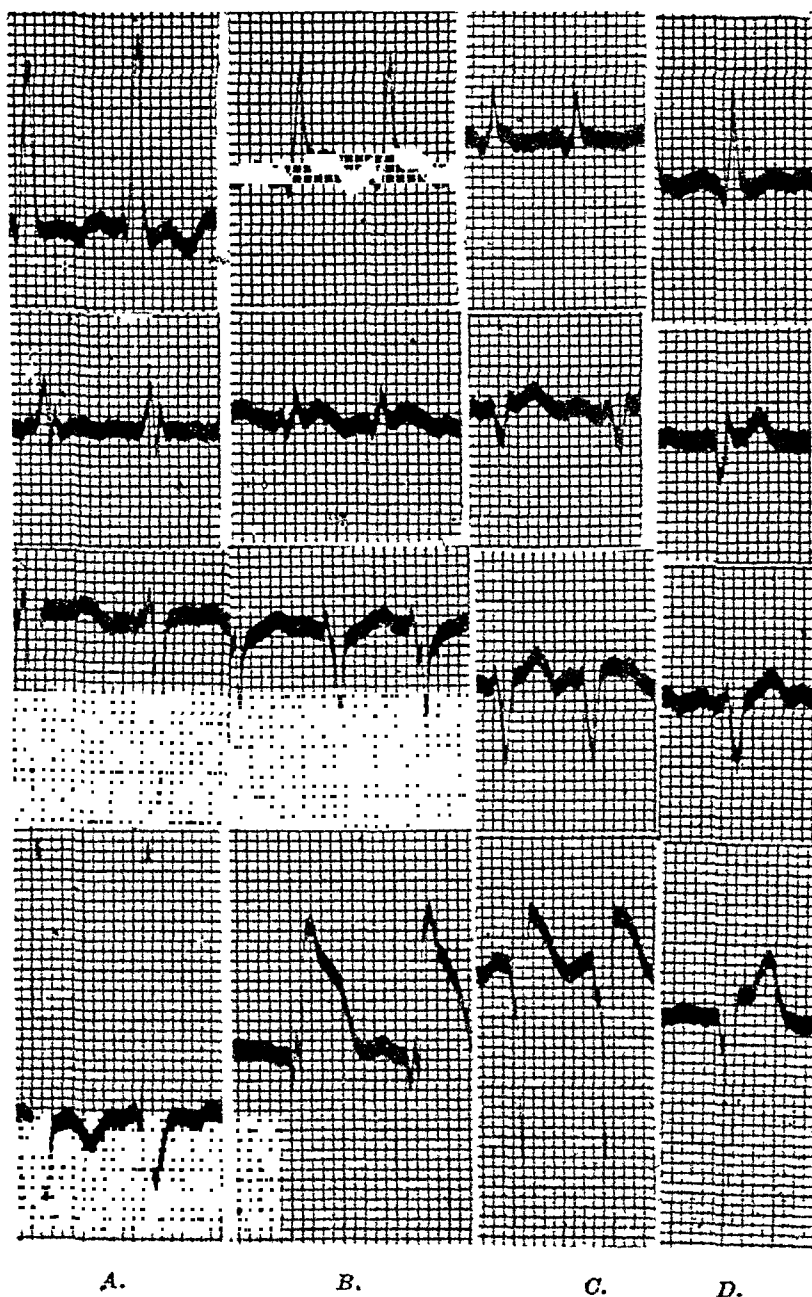


Fig. 1 (Case 2).—A, Before infarction. B, Less than twenty-four hours after the attack. C, Two days after the attack. D, Five days after the attack. In this and in all subsequent figures, the leads are I, II, III, and IV, from above downward.

The lesion in Case 4 involved the anterior wall and its endocardial surface, the anterior portion of the septum, and the lateral wall slightly, but not anywhere did it reach the epicardial surface, except in a small area on the lateral wall. The record before infarction (Fig. 3, A) showed left axis deviation of the QRS complex with a Q-S₂ wave, an inverted T₁ wave of the coronary type, and a diphasic (\pm) T₄ wave.

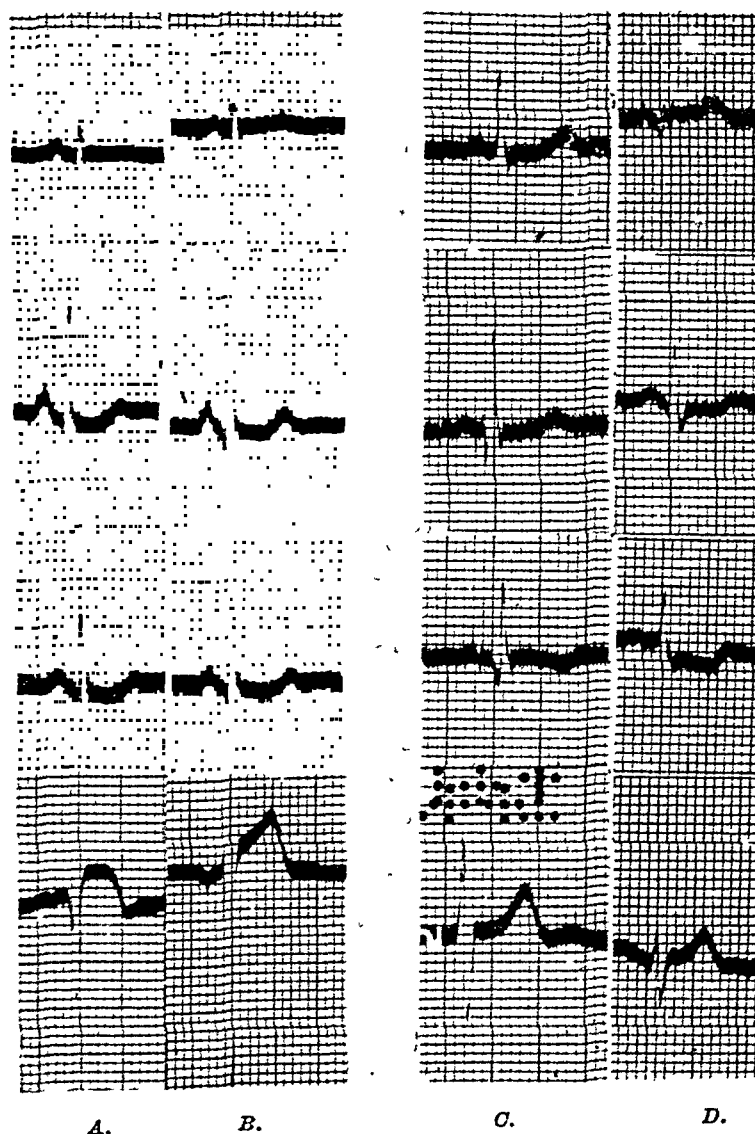


Fig. 2 (Case 5).—A, Three days after infarction. B, Six days after the attack. C, (Case 3). Before the infarction. D, Record three days after the attack.

On the day of the infarction, Fig. 3, B was obtained. The QRS complex was essentially unchanged; the S-T₁ junction was depressed and the T₁ wave was inverted; the S-T₂ junction was slightly downward, with the T₂ wave positive; the S-T₃ junction was elevated and the T₃ wave was upright; the S-T₄ segment was depressed and the T₄ wave was inverted.

These S-T- and T-wave changes are the opposite of those expected with an anterior wall infarct. It has been suggested on theoretical grounds by Bayley⁶ and others that such a reversal of direction may be due to the infarct affecting only the endocardial portion of the anterior wall. The S-T- and T-wave changes closely resemble the appearance found in the acute stage of lateral infarction as described by Wood, Wolferth, and Bellet and also that seen after exercise tests and anoxemia tests.

Three days later, the QRS complex had changed markedly in Lead III (Fig. 3,C). The Q-S₂ deflection had been replaced by a small R wave and a large S deflection, and the axis was now strongly toward the left. At this time there was an inverted T₁ deflection of the coronary type with a slightly inverted T₂ wave, and in Lead III a normal S-T junction with an upward T wave. The precordial lead showed a large Q wave, a well-developed R deflection, a slightly elevated S-T junction, and an inverted T wave. Four later records, the last of which was obtained four days before death (Fig. 3,D), showed essentially similar features. In the healing stage, the record in the limb leads resembles the

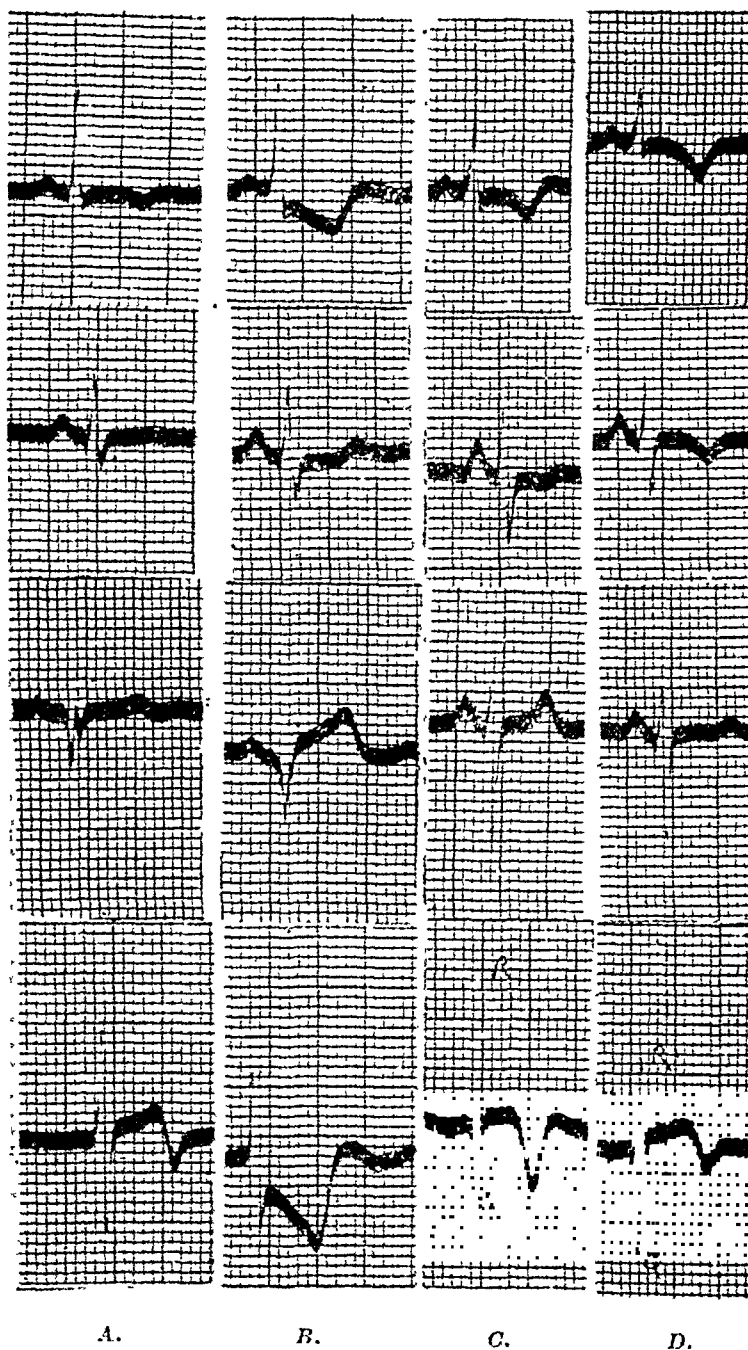


Fig. 3 (Case 4).—A. Record before infarction. B, Record on the day of the attack. C, Record on the third day after the attack. D, Record on the sixteenth day after the attack.

picture in anterior infarction, but there is also some resemblance to the pattern associated with hypertrophy and left ventricular strain. In the precordial lead, the picture is typical of the healing stage of anterior infarction. In the acute stage, the record did not suggest a diagnosis of anterior infarction.

In Case 5 there was an infarct which involved only the anterior portion of the septum, coming to the surface beneath the endocardium in the left ven-

tricle and somewhat in the right ventricle but the anterior wall or the epicardial surface of the heart was not reached. In spite of the lack of epicardial involvement, the record of the acute stage (Fig. 2,A) failed to show the R wave in the precordial lead, where a large Q-S deflection and typical elevation of the S-T junction were present. In the limb leads the appearance was not characteristic of an acute infarct but showed an isoelectric T₁ wave and a depression of the S-T segment with upward T waves in Leads II and III, an appearance like that induced by exercise and by anoxemia in susceptible hearts. In this case the record as a whole was diagnostic of acute infarction only because of the absence of the R wave and the characteristic appearance of the S-T and T deflections in Lead IVF.

It is of especial interest that, with this purely septal infarct, there is a Q-S deflection—absence of the R wave—in the precordial lead, such as has been attributed to damage of the whole thickness of the anterior wall of the ventricle,¹ and that the T wave in this lead had the appearance supposed to result from damage to the superficial anterior layers of the myocardium.

Of the three cases with incomplete anterior wall infarction with septal involvement, Cases 2 and 5 had a Q-S deflection in the precordial lead, as would have been expected with a lesion involving the whole thickness of the anterior wall, and the T wave had the appearance expected with necrosis of the superficial anterior layers of the myocardium. Case 4 showed normal R and S waves in Lead IV of the early record, but the later record showed a large Q wave followed by R and S deflections as would be expected in a heart such as this with remaining viable subepicardial fibers above necrosis reaching to the endocardium.² The early record had the S-T and T deflections of Lead IV opposite in direction to what would have been expected with an acute anterior infarction, but the later records in this lead were typical of anterior infarction in the healing stage. Case 2 alone showed the classical pattern of anterior infarction in both limb leads and precordial leads. Cases 3, 4, and 5 showed S-T- and T-wave abnormalities in the limb leads of the earliest records like those commonly seen after exercise and anoxemia tests. The precordial lead in the first of these cases was normal; in the second it resembled that seen with exercise and anoxemia tests; and, in the third, it suggested anterior infarction.

There was one recent lateral wall infarct (Case 6) which extended into the posterior wall and showed S-T- and T-wave changes like those associated by Wolferth and his associates⁷ with the acute stage of lateral infarction. Case 7 showed an old healed lateral infarct with the inverted T₁ and T₂ waves, and preservation of the R₁ wave which would be expected according to Wolferth's descriptions.

There were five cases with a typical posterior, i.e., diaphragmatic, situation of the infarct, two (Cases 10 and 11) with, and three (Cases 8, 9, and 12) without septal involvement. Three of these cases (Cases 9, 10, and 11) afforded an opportunity to observe the effect of the infarct upon the electrical axis of the QRS complex. A comparison of the records, before and after infarction (compare Figs. 4,B and C, and 5,A and B), showed that, in all three, the electrical axis of the QRS complex was rotated toward the right, though it still remained within the normal sector.

Cases 8, 10, and 11 each had an infarct involving the complete thickness of the posterior wall and all had a large Q₂ wave.

The records of Cases 10 and 11, with complete posterior wall and septal involvement, showed a large Q₂ wave and the typical acute S-T- and T-wave

changes associated with posterior infarction, with marked elevation of the S-T junction in Lead III and depression of the S-T junction in Leads I and IV. Case 11 (Fig. 4, *C* and *D*) showed a total inversion of the T wave in Lead IV which is not ordinarily described as a feature of posterior infarction. Case 8 (Fig. 4, *A*), with a complete mural lesion without septal involvement, showed the S-T junction and the T waves in Leads II and III of the subacute or healing type (coronary T waves), but it must be borne in mind that the record was not obtained until five days after the attack occurred. An earlier record might have shown more typical acute S-T- and T-wave changes. The precordial lead had negative S-T and T deflections of a nonspecific appearance, somewhat like the later record of Case 11 (Fig. 4, *D*).

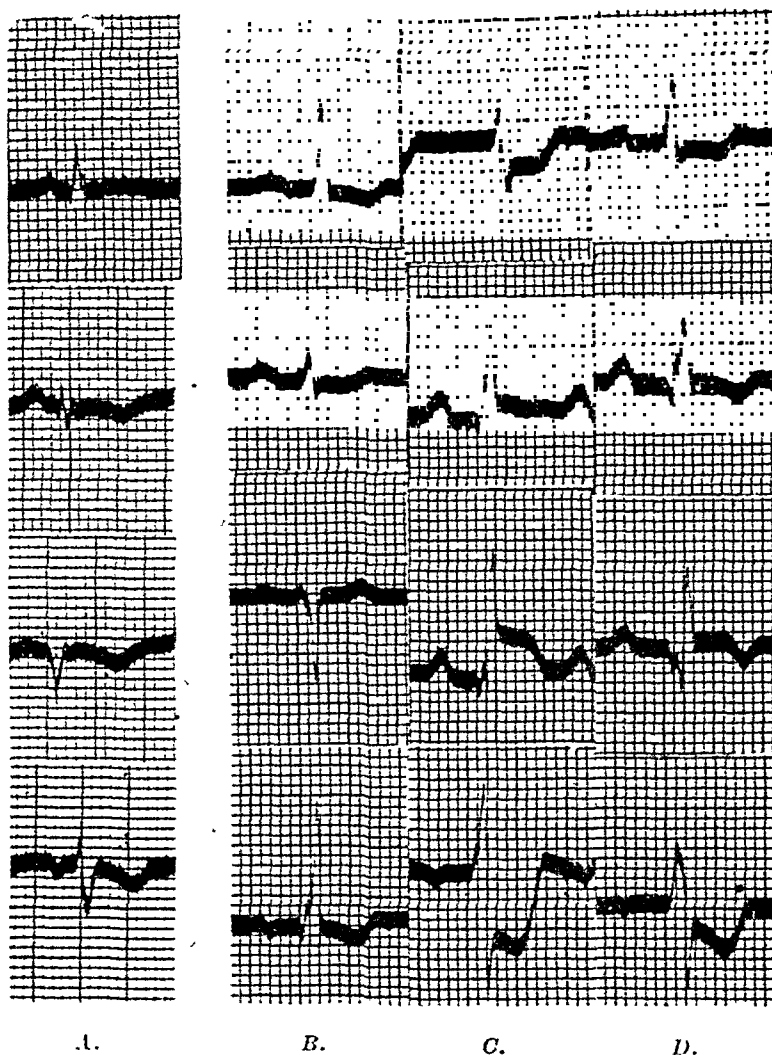


Fig. 4 (Case 8).—*A*, On the fifth day after infarction. *B*, (Case 11), Before the infarction. *C*, On the day of the attack. *D*, On the second day after the attack.

There were two cases with an incomplete posterior wall lesion (Cases 9 and 12). Case 9 showed recent subendocardial and posterior wall necrosis, without involvement of the subepicardial layers or septum, and an old anterior septal scar. The record before the infarction (Fig. 5, *A*) showed T-wave changes due to the old anterior lesion. The record taken the day after the infarct (Fig. 5, *B*) showed in the limb leads a small Q_s deflection and a minimal elevation of the S-T₂ junction, while in Lead II there was a suggestion of the coronary T wave usually associated with the healing stage of infarction. The precordial lead developed a small R' wave but had a normal appearance of the S-T segment and T wave, although the S-T segment was at a lower level than before the infarct. In later records the coronary T₂ wave persisted, the S-T junction returned to the zero level in Lead III, and to slightly above it in

Lead IV (Fig. 5,C). The absence of a large Q_s wave in this case might be ascribed to the fact that the old area of degeneration in the anterior part of the septum had prevented the development of a large Q_s deflection by removing the potentials normally supplied by this area. The S-T- and T-wave changes in the limb leads were fairly typical of those due to posterior infarction, though not especially suggesting an acute lesion.

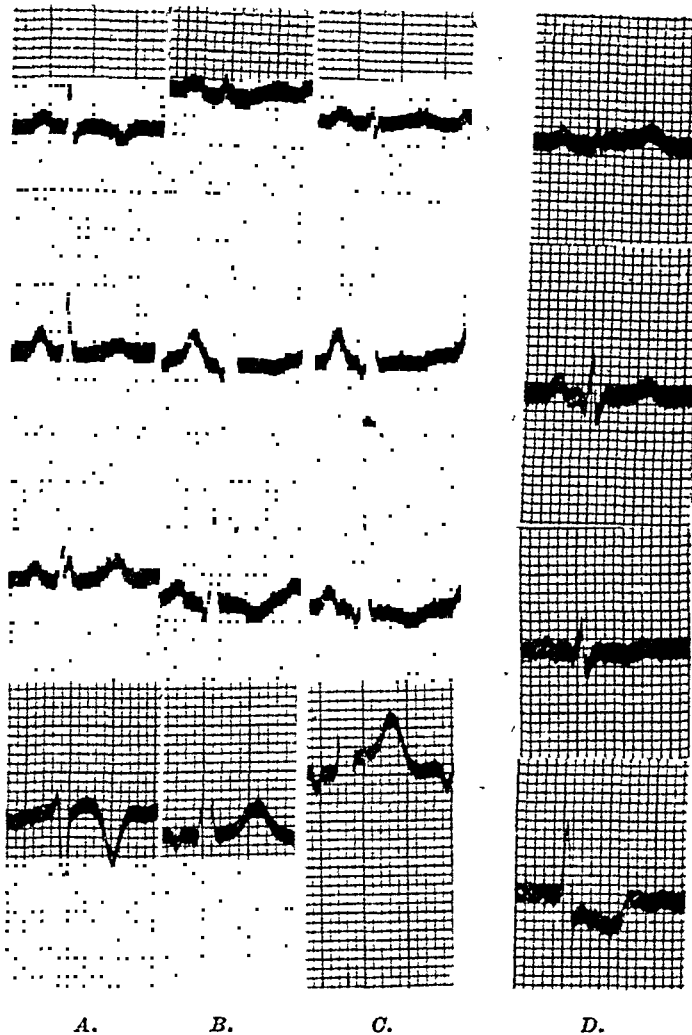


Fig. 5 (Case 9).—A, Before the infarction. B, On the first day after the attack. C, On the fifth day after the attack. D, (Case 12), on the eighth day after infarction.

Case 12 had a large intramural posterior wall infarct with only very small areas of subepicardial and subendocardial involvement, each about 4 by 8 millimeters. The record (Fig. 5,D), taken two days after the infarction, revealed nothing characteristic of the infarct picture in the limb leads while the precordial lead showed marked negativity of the S-T segment and of the T wave, as is occasionally seen after posterior infarction associated with typical limb lead patterns (e.g., Fig. 4,D). Such a T_4 wave is also seen associated with the limb lead features of the exercise reaction. In Case 12, however, without typical limb lead patterns, the appearance of Lead IV is not suggestive of acute infarction. In the limb leads there is a very slight elevation of the S-T junction in Lead I and a slight depression of this part of the curve in Lead III. The amplitude of these deflections is very small. This deflection is in the opposite direction to what one would expect from an acute posterior wall lesion.

DISCUSSION

A careful study of the site and extent of the infarct and a correlation of this with the QRS-, S-T-, and T-wave changes in twelve cases have revealed certain features that are worthy of emphasis:

Of six cases with records before and after infarction, there were three cases with an anterior lesion. One showed a shift of the axis of the QRS complex toward the right; one showed no shift of the axis; and the other showed a shift toward the left. There were three cases with a posterior lesion, and all three showed a shift of the axis of the QRS complex toward the right.

Of two anterior wall infarcts with septal involvement (Cases 2 and 5), one was associated with typical acute S-T-changes in the limb leads and in the precordial lead and both with the typical Q-S deflection in the precordial lead. A Q-S deflection in the precordial lead would not have been expected in either of these cases because the heart did not show involvement of the subepicardial fibers, the feature that has been supposed to give rise to this change in the record.

The importance of necrosis of the anterior part of the septum in relation to changes in the precordial lead is further indicated by the fact that the one case of anterior infarction without such septal involvement (Case 3) failed to show any abnormal features in this lead, while the other four cases of anterior infarction did have septal involvement and were associated, either early or later, with the QRS-, S-T-, and T-wave changes in Lead IV, considered typical of anterior infarction.

Of the four anterior infarcts without subepicardial necrosis, only one (Case 2) was associated with the typical QRS-, S-T-, and T-wave changes of acute anterior infarction in both limb leads and precordial lead. Case 5 showed typical acute changes in the precordial lead alone. Case 4 showed a peculiar appearance in the first record but in the records of the third day after infarction and later both limb leads and precordial lead suggested anterior infarction. Case 3 was not typical of infarction in the limb leads, and the precordial lead was normal. Cases 3, 4, and 5 showed S-T- and T-wave changes in the limb leads of the early records like those seen after exercise and anoxemia tests.

There were two complete posterior wall infarcts with septal involvement (Cases 10 and 11) and these had typical acute S-T- and T-wave changes in both limb leads and precordial lead. There was one complete posterior wall infarct without septal involvement (Case 8) and on the fifth day after the attack this case showed S-T- and T-wave changes in the limb leads like those associated with a healing posterior infarct. The precordial lead had a depressed S-T segment and an inverted T wave, unlike the usual appearance in the healing stage of posterior infarction.

Two cases with posterior wall infarction without subepicardial involvement and also without septal involvement (Cases 9 and 12) failed to show typical acute S-T- and T-wave changes in the limb leads. In the precordial lead of Case 9 there was a normal S-T segment and T wave, and, in that of Case 12, the S-T segment and T wave resembled the usual exercise test pattern, though of a type occasionally accompanying the typical limb lead pattern of acute posterior infarction.

A lesion of either anterior or posterior wall, involving also a part of the adjacent septum, occurred five times (Cases 1, 2, 4, 10 and 11). It was associated, except in Case 4, with the typical S-T- and T-wave changes of the acute phase of the infarction curve both in the limb leads and the precordial lead. The

changes were of the anterior or the posterior type, in conformity with the mural involvement. Mural necrosis without septal involvement occurred in four cases, none of which had the typical S-T- and T-wave changes of acute infarction (Cases 3, 8, 9, and 12). In the five cases with posterior lesions, typical acute S-T- and T-wave changes, both in limb leads and in the precordial lead, were found only in the presence of complete transmural and posterior septal involvement (Cases 10 and 11). In the five with anterior lesions, typical acute S-T- and T-wave changes were found both in limb leads and in the precordial lead in only two cases (Cases 1 and 2). Both of these had septal involvement, one with complete transmural necrosis, the other with incomplete involvement of the wall, lacking necrosis of the subepicardial layers.

The importance of involvement of the septal muscle in relation to the appearance of the acute S-T-segment changes of infarction in both the anterior and posterior situations is surprising, for it has been our opinion that damage to the subepicardial muscle caused the typical S-T elevation.

A $Q-S_4$ deflection occurred once with involvement of the septum and entire thickness of the anterior wall (Case 1), once with anterior wall and septal involvement without the epicardial surface apparently being affected (Case 2), and once with only the septum and the endocardial surface showing damage (Case 5). One would expect involvement of the whole anterior wall to accompany the appearance of the $Q-S_4$ deflection, but in these cases the only constant pathologic feature is necrosis of the anterior part of the septum and subendocardial layers. A large Q_4 wave with an R and S deflection was found in the later records of Case 4, as would have been expected with the deeper layers of the anterior wall affected, without subepicardial degeneration. These waves, however, did not appear in Case 2 which showed a similar pathologic appearance. The apparent importance of the septal muscle in relation to the appearance of a $Q-S_4$ deflection is surprising in view of our belief that a lesion affecting the whole depth of the anterior wall is necessary to abolish the preintrinsic R deflection. What has been said previously about the lack of relationship between the structural appearance of heart muscle and its ability to produce a normal electrical curve must be recalled in relation to the disappearance of the R deflection from the precordial lead. It is possible that apparently intact muscle fibers might fail to give a normal electrical reaction, but it is noteworthy that in Case 5 the necrotic area did not involve any part of the anterior wall of either ventricle. It would seem surprising that a physiologic change would extend so far from the necrotic area that was found.

A large Q_3 deflection occurred twice with a complete lesion of the posterior wall and septum (Cases 10 and 11) and once with a complete posterior wall lesion but without the septal involvement (Case 8). A small Q_3 deflection appeared once with an incomplete posterior wall lesion, without the epicardial surface and the septum, but there was also marked old scarring of the anterior septum, which might have prevented the appearance of a wave of larger size. Complete transmural involvement of the posterior wall was the only constant pathologic finding in the cases with a large Q_3 deflection. A large Q_3 deflection, previously present, was twice abolished by an infarct of the anterior wall, once occurring with, and once without, septal involvement.

The apparent dependence of the Q_3 deflection upon posterior mural lesions, rather than upon posterior septal lesions is of interest. The abolition of a Q_3 deflection, previously present, by a recent intramural infarct in the anterior wall, without septal involvement, also has an important bearing upon our concept of the genesis of the Q_3 deflection. It indicates that the muscle of the anterior

wall has a part in the appearance of the Q_3 deflection in cases with posterior infarction, a fact sometimes lost sight of in theoretical discussions of the cause of this wave.

The resemblance of the limb leads of Cases 3, 4, and 5, with anterior infarction without subepicardial involvement to those records seen after anginal attacks, exercise tests, and anoxemia tests is of interest. The reason for the similarity of these records may be that in both types of cases there is a limitation of the necrosis, on the one hand, and the ischemia, on the other, to the subendocardial and intramural layers of the wall. That cases of angina may have lesions of this character has been demonstrated by Büchner,⁸ who found areas of subendocardial necrosis in patients dying after attacks of anginal pain without the typical clinical features of infarction, such as fever, leucocytosis, and increased sedimentation rate. Case 12, with an incomplete posterior lesion, showed T-wave changes of this type in the precordial lead alone.

It is a striking fact that the incomplete mural infarcts, without involvement of the subepicardial layers of the ventricular wall, rarely have records that definitely resemble the typical acute infarction curve of anterior or posterior type. In only one of the six cases (Case 2) was the record typical of such a diagnosis. In Case 5, the precordial lead made the diagnosis probable, and, in Case 4, the first record suggested an acute lateral infarct. In Cases 3, 9, and 12, neither the limb leads nor the precordial lead suggested acute infarction.

There is no definite pattern by which these incomplete mural infarcts can be recognized, for Case 2 demonstrates that they may even give rise to a typical infarction record, but the frequency of S-T- and T-wave patterns like those appearing after exercise and anoxemia tests is worth stressing and also that these patterns may be found in either the limb leads or in Lead IVF, but rarely in both.

One case of acute lateral infarction was observed to have the electrocardiographic appearance described by Wolferth, as was also a case with an old healed lateral infarction.

A search of the literature reveals but three autopsied cases comparable to those of our series and with an electrocardiogram including Lead IV. Langendorf and Kovitz⁹ reported two cases of anterior infarction without the subepicardial layers being necrotic and with septal involvement. Neither of these cases had records suggesting acute infarction. One of them showed in the limb leads a normal S-T junction, an upward T_1 deflection, and inverted T_2 and T_3 deflections with low voltage. In Lead CF_2 there was a large Q-S deflection, and a normal S-T segment and T wave, while in Lead CF_4 , the R wave was present, the S-T segment was normal, and the T wave was coved and inverted. The other case showed a typical exercise pattern in the limb leads with depressed S-T₁ and S-T₂ segments and upward T waves. Lead CF_2 was normal and CF_4 had a normal R wave and normal S-T junction but an inverted T wave. Price and Jams¹⁰ reported a case with posterior infarction involving only the subendocardial layers of the posterior wall and septum and "extending on to the anterior wall of the left ventricle in its middle and apical portions. This anterior portion gradually left the subendocardial layers to become intramural near the apex." The record of this case resembled those of the healing stage of posterior infarction (e.g., Fig. 4,D). The limb leads showed minimal S-T depression in Lead I with an upward T deflection: the T_2 wave was coved and inverted; the S-T₃ junction was +0.5 mm., and the T_3 deflec-

tion was inverted. A large Q_3 deflection was present. Lead IVR showed a normal R wave, a normal S-T segment, and an inverted T wave.

The findings in these three cases are at variance with ours in that the two anterior infarcts with septal involvement, without necrosis of the subepicardial layers of the anterior wall, did not have a Q-S deflection in Lead IV. One of our cases, in fact, did not show this in the early record but did have a large Q_4 wave in later ones. Disagreement was also found in the case with posterior infarction without a complete transmural lesion, which, nevertheless, had a large Q_3 deflection. They were in agreement with our findings in that one of the anterior cases had the appearance in the limb leads commonly seen after exercise and anoxemia tests and that all three lacked subepicardial necrosis and failed to show the typical electrocardiographic features of acute infarction.

SUMMARY AND CONCLUSIONS

It is difficult to summarize these observations because of the many electrocardiographic features that must be considered. Certain associations have appeared definite enough to warrant emphasis, in spite of the small number of cases. In this connection, however, the relation between the structural integrity of the myocardium and its ability to produce a normal electrical curve must be considered. There may be a depression of the physiologic activity of muscle without either gross or microscopic anatomic changes but, as far as structural alterations are concerned, the following conclusions seem justifiable:

After either anterior or posterior infarction, but more uniformly after the latter, there is a rotation of the electrical axis of the QRS complex toward the right.

The typical S-T- and T-wave changes, that we have come to associate with acute infarction, occur most often in the presence of necrosis of the anterior or posterior wall, including a portion of the adjacent interventricular septum. Mural necrosis without septal involvement may be associated with these typical changes, but not as constantly.

The typical S-T- and T-wave changes in the limb leads and the precordial lead, and the Q-S deflection in the precordial lead, occasionally appear after anterior infarction, even without necrosis of the subepicardial layers of the wall.

The Q-S or Q deflection in the precordial lead is associated with necrosis of the anterior part of the septum and may be present when this part of the septum is affected, even without involvement of the anterior wall.

A large Q_3 deflection may appear without the presence of necrosis in the posterior part of the interventricular septum, if there is a complete transmural lesion.

The records of cases with anterior infarction without subepicardial necrosis somewhat resemble those seen after exercise and anoxemia tests and during anginal attacks.

The records, after either anterior or posterior infarction without involvement of the subepicardial layers of the wall, rarely have an appearance that closely resembles the typical acute infarction curve of anterior or posterior type.

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TRANSIENT "0" DIASTOLIC BRACHIAL PRESSURE (INDIRECT), ASSOCIATED WITH NORMAL OR ELEVATED POPLITEAL PRESSURE, TACHYCARDIA, AND NERVOUS TENSION

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IN THE course of the routine examinations of men between the ages of 18 and 45 years for induction into the Armed Forces* of the United States, a cardiovascular syndrome, hitherto undescribed, was observed in thirty-eight examinees exhibiting a pronounced degree of nervous tension. In addition to the nervous element, the syndrome was characterized by transient "0" diastolic brachial pressure (indirect method), normal or elevated popliteal pressure, and tachycardia.

In the initial cases it was felt that perhaps we were observing instances of functional aortic insufficiency (despite certain features to the contrary to be mentioned later); consequently blood pressure readings were recorded in the lower extremities. The desirability of these latter determinations was based on the observations of Hill, Flack, and Holtzmann,¹ Hill and Rowlands,² and Loewenberg³ who have reported the occurrence, in organic aortic insufficiency, of a more pronounced discrepancy between the brachial systolic pressure and the popliteal systolic pressure than occurs physiologically⁴ (Hill's sign^{5, a}). Loewenberg³ has recently stressed the importance of this sign in distinguishing functional from organic aortic insufficiency. Unfortunately, several earlier cases observed are not included in this report inasmuch as the significance of the

These observations were made during the period in which the author served as cardiologist on the Examining Board of the Armed Forces Induction Station, Tacoma and Seattle, Washington.

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*All branches of service; the majority represent examinations for induction into the Army.

observations was not clear at the time, and no detailed data were recorded. It was not until several instances had been encountered that we were prompted to perform more complete studies. Inasmuch as no reference to this syndrome could be found in the literature, the observations are reported.

PROCEDURE

Brachial arterial pressure was determined* by the indirect method in the antecubital space; a standard mercury manometer with a cloth covered, 13-cm. (width) rubber cuff, hook-on type, was employed. The examinee was in the sitting position, with his arm slightly flexed and with his forearm at the level of the heart. Readings were recorded by the auscultatory method in accordance with the recommendations of the Committees for the Standardization of Blood Pressure Readings of the American Heart Association and of the Cardiac Society of Great Britain and Ireland.⁶ The routine procedure was to record the level of the diastolic pressure at a well-defined fourth phase (muffling of the sounds), or, if absent, at the fifth phase (disappearance of the sounds). None of the examinees included in this report exhibited a clear, definite transition, although in several instances a faint change was audible. In this regard it might be mentioned that considerable uncertainty still exists as to which of the two phases is the more reliable index of diastolic pressure.^{7, 8} The popliteal blood pressure was determined in a similar manner in the popliteal fossa; readings were recorded both in the standing and prone positions in all examinees exhibiting a diastolic brachial pressure of "0." The cuff was the same as that employed in the upper extremity. Circumstances precluded the use of a wider cuff. It is doubtful, however, with the employment of a cuff lined with metal ribs and a hook-on device which prevented slipping or bulging of the rubber sac, if this factor could have exerted any significant influence on our basic observations.⁴ Each examinee was completely naked, and the examining room was kept at a comfortable temperature level. No physical effort preceded the blood pressure determinations for at least thirty minutes other than the effort of undressing and that associated with a gradual, short move in line. The examinations were conducted in the morning and early afternoon. In the majority of instances, there was no food intake for several hours preceding the examinations. The brachial blood pressure determinations were part of the routine induction examination. The popliteal examination was performed when the brachial diastolic pressure was recorded as "0." An examinee exhibiting a brachial diastolic pressure of "0" was reassured, encouraged to relax and given a rest period (seated) of from five to fifteen minutes. Then the blood pressure readings were repeated. If still unchanged, he was told to resume his seat, and the readings were repeated at ten- to twenty-minute intervals generally, until the brachial diastolic pressure had attained a level of 60 mm. Hg or over. One case was observed in which a normal brachial diastolic level was not attained at the end of one and three-fourths hours. This examinee was in a state of marked nervous tension, and although circumstances prevented a longer rest period, it was felt, after complete cardiac studies, that this case represented a similar example of the phenomenon described. This man is not included in the group reported. Blood pressure determinations were frequently repeated in the contralateral arm and leg.

*Routine blood pressure determinations were performed by trained Medical Department enlisted men, instructed in the errors of technique, who referred all examinees exhibiting this phenomenon to the author for repeat readings and cardiovascular studies.

RESULTS

Thirty-eight examinees exhibited a relatively uniform pattern, the outstanding feature of which was a "0" brachial diastolic pressure, transitory in nature. The data are presented in Table I. The brachial systolic pressure on initial examination ranged from 118 to 250 mm. Hg, and averaged 159.1. The popliteal systolic pressure in the prone position ranged from 162 to 300 mm. Hg; the average was 202.3. The popliteal diastolic pressure in the prone position ranged from 68 to 144 mm. Hg, and averaged 101.9. In the standing position, the popliteal systolic pressure ranged from 190 mm. Hg (the only reading below 200) to 300 mm. Hg, the latter noted in six men; the average was 247.3. The diastolic pressure in the popliteal artery in the standing position ranged from 98 to 246 mm. Hg; the average was 159.7. The lowest prerest heart rate noted was 90; only two were below 100. The highest rate was 168. The average was 127.4. The heart rate was determined in the sitting position. Rest periods necessary to bring about return of the brachial diastolic pressure to 60 mm. Hg or above (exclusive of the examinee mentioned previously who did not exhibit a return to normal at the end of one and three-fourths hours) ranged from five to ninety minutes, and averaged 25.8 minutes. Detailed data, together with the changes in these values associated with the return of the brachial diastolic pressure readings to values of 60 mm. Hg or over, are presented in Tables I, II, and III.

Four groups of examinees could be delineated (Table I): Group 1, which includes Cases 1 through 13, represents those men whose brachial systolic pressure, before rest, did not exceed 140 mm. Hg and whose brachial systolic and diastolic pressures after rest did not exceed 140 and 90 mm. Hg, respectively. This group probably can be safely eliminated as being nonhypertensive. Group 2 includes Cases 14 through 18 (five men) and represents those men whose prerest or postrest systolic brachial pressure exceeded 140 mm. Hg but did not exceed 150, and whose post-rest brachial diastolic pressure did not exceed 90. The inclusion of this as a separate group is made because of the existing uncertainty as to the blood pressure levels constituting hypertension.⁹ The United States Army¹⁰ employs 150 mm. Hg, systolic, and/or 90 mm. Hg, diastolic, as the upper limits of normal for inductees. Others regard 140 mm. Hg and/or 90 mm. Hg, systolic and diastolic, respectively, as the upper limits of normal. Group 3 includes Cases 19 through 27 (nine men) and incorporates those examinees whose postrest brachial systolic and diastolic pressures did not exceed 140 and 90 mm. Hg, respectively, but whose prerest brachial systolic pressure exceeded 150. Group 4 includes Cases 28 through 38 (eleven men) who exhibited postrest brachial readings exceeding 150 mm. Hg, systolic, and/or exceeding 90 mm. Hg, diastolic. The postrest brachial pressure, that is, the blood pressure following recovery of the diastolic pressure to normal levels, is used as the principal basis for the delineation of the cases into four groups inasmuch as it is obvious that it represents a closer approximation to the actual blood pressure than does the initial (prerest) reading.

It is interesting that following rest only two examinees revealed a brachial diastolic pressure exceeding 90 mm. Hg (although three were observed to reach this level), and in view of the frequency with which blood pressure lability was previously observed in Army⁹ and Navy¹¹ examinees, and the evident nervous state of these men, it is exceedingly questionable if the majority of the examinees in Group 4 can be classed as having true hypertension. The influence of other factors on normal arterial pressure has been elaborated repeatedly.^{9, 12-15}

Cases 37 and 38 are probably the only examinees who can be justifiably regarded as hypertensive, and yet blood pressure readings of such levels have previously been demonstrated⁹ to occur transiently in hyperexcitable Army inductees with markedly labile vasomotor mechanisms. For this reason these groups have all been incorporated, as subdivisions, in one table rather than tabulated separately. None of the examinees, including Examinees 37 and 38, were demonstrated to have organic heart disease following complete studies.

TABLE II. DIRECT COMPARISON BETWEEN INITIAL (PREREST) AND POSTREST READINGS

	BRACHIAL B.P. (MM. HG)		POPLITEAL B.P. (MM. HG)				HEART RATE†
	SITTING		PRONE		STANDING		
	SYSTOLIC	DIASTOLIC	SYSTOLIC	DIASTOLIC	SYSTOLIC	DIASTOLIC	
	SYSTOLIC	DIASTOLIC	SYSTOLIC	DIASTOLIC	SYSTOLIC	DIASTOLIC	
Initial (prerest) readings:							
Lowest	118	“0”	162	68	190	98	90
Highest	250	“0”	300‡	144	300‡	246	168
Average	159.1	“0”	202.3	101.9	247.3	159.7	127.4
Postrest readings:							
Lowest	116	60	145	68	170	104	76
Highest	220	112	278	124	300‡	210	148
Average	148.1	75.2	189.8	94.8	237.1	152.6	104.7
Average change* from pre- rest to postrest values	-11.0	+75.2	-12.5	-7.1	-10.2	-7.1	-22.7

*- represents decrease.

+ represents increase.

‡Sitting heart rate.

‡Maximum value obtainable with mercury manometer employed.

TABLE III. RESPONSE OF EXAMINEES TO RISE OF THE DIASTOLIC PRESSURE FROM "0" TO 60 MM. HG OR ABOVE

	BRACHIAL SYSTOLIC PRESSURE (SITTING)	POPLITEAL B.P.				HEART RATE ⁺
		PRONE		STANDING		
		SYST.	DIAST.	SYST.	DIAST.	
Number of examinees exhibiting:						
Decrease	27	33	29	32	29	37
No change	4	2	3	3	4	1
Increase	7	3	6	3	5	0

*Sitting heart rate.

It might be well to mention, at this point, that 300 mm. Hg was the highest value obtainable with the mercury manometer employed. However, inasmuch as the number of these readings was small, and the probability that the unknown excess was not great, it is unlikely that the averages cited are altered to any significant degree. In any event it is evident that they could have little effect upon the basic observations.

"Peripheral phenomena" (Lewis) exhibited considerable variability (Table I). The most common was the "pistol-shot" sound, occurring in fifteen examinees; in all but two instances they disappeared following return of the brachial diastolic pressure to normal. Next in frequency was the Corrigan pulse, observed in five men. Capillary pulsation was clinically demonstrable in only two instances. Both the Corrigan pulse and capillary pulsation disappeared following return of the brachial diastolic pressure to normal. Duroziez' murmur was not encountered.

TABLE IV. AGE DISTRIBUTION OF EXAMINEES*

AGE (YRS.)	18 TO 20	21 TO 25	26 TO 30	31 TO 35	36 TO 40	41 TO 45
NUMBER OF CASES	15	12	8	2	1	0

*See text for comment on relation to general age groups represented by total examinees.

It will be noted in Table IV that the vast majority of the examinees exhibiting the syndrome were in the younger age groups. There were fifteen between 18 and 20 years of age, twelve between 21 and 25, eight between 26 and 30, two between 31 and 35, one between 36 and 40, and none between 41 and 45 years of age. This proportion far exceeds the general age proportions represented by the examinees, and seems to indicate a predilection for younger persons. A direct comparison with the precise age proportions of the total number of examinees cannot be given for military reasons.

DISCUSSION

The return of the diastolic brachial pressure from "0" to normal or above occurred relatively rapidly in the majority of the examinees. In several instances the sounds were observed to appear and disappear while the cuff remained deflated and the mercury maintained at "0" level, or while the examinees rested with no cuff applied to the arm and with care exercised to avoid compression of the brachial artery with the diaphragm of the stethoscope. It should be recalled that these men were completely undressed, and an arterial constrictive factor was thus eliminated. In some cases a gradual climb in diastolic brachial pressure was noted as manifested by readings obtained on repeated determinations. The length of time required for the "0" diastolic pressure to return to 60 mm. Hg or more appeared to bear no direct relationship to either the cardiac rate or the height of the systolic pressure associated with the "0" diastolic pressure.

The mechanisms involved in the genesis of the syndrome are difficult to explain. Katz¹⁶ suggests this phenomenon may resemble that which arises occasionally in the upper extremities in free aortic regurgitation in which a systolic murmur and thrill occur in these extremities when they are raised above the head. He feels that in our examinees, either through autonomic (nervous) effects or epinephrine release, the result of fear and excitement, stroke output is increased and peripheral vasodilatation occurs. The effect of the inadequately filled vessels and high pulse pressure is to create sufficient turbulence, as the anacrotus becomes steeper approaching the periphery, to produce audible brachial vibrations despite the existence of zero pressure in the blood pressure cuff.

An interesting hypothesis which merits consideration is the operation of an adrenergic mechanism based upon Cannon's^{17, 18} theory of epinephrine release in fear. Goodman and Gilman¹⁹ state that, apparently, when epinephrine is absorbed slowly, as from hypodermic injection, vasodilatation occurs in the skeletal muscles. This has been demonstrated by Blumgart,²⁰ Starr and his associates,²¹ and others.²²⁻²⁵ It would be presumed that the nervous tension exhibited by the examinees was an expression of fear, which, stimulated, increased adrenal activity; this resulted in the release of small amounts of epinephrine into the circulation, producing arterial dilatation in the muscle bed of the upper extremities and initiating certain compensatory reflex mechanisms which maintain normal vascular tone or bring about vasoconstriction in the lower extremities, to counteract the effects of the vasodilatation in the upper extremities in order that physiologic blood pressure levels and adequate cerebral flow be maintained. There also appears to be evidence suggesting that, under certain conditions, the lower extremities may be more responsive to vasoconstrictor influences than the upper extremities. Downman and his associates,²⁶ employing decerebrate and anesthetized cats, in the horizontal position, have recently observed that in some of the animals various sensory stimuli brought about reflex

vasoconstriction in the paws of both the hind legs and the forelegs, but in others the vasoconstrictor response was confined to the paws of the hind legs only. They regard the anatomic plan of the reflex as the same in man. Evans and Stewart²⁷ have noted a more pronounced degree of reduction in the skin temperature of the foot than of the hand as a result of smoking, apparently due to a more marked vasoconstriction in the skin of the lower extremities than in the upper; however, the cutaneous response may not represent the response in the muscle bed. Fig. 1 serves to present schematically the two divergent mechanisms in the upper and lower extremities.

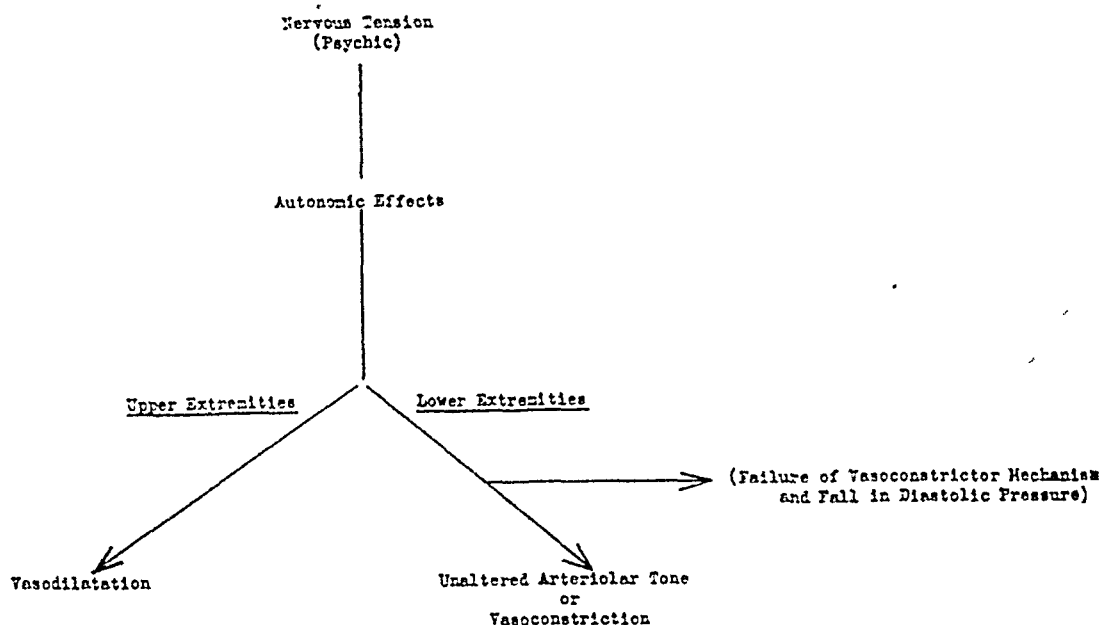


Fig. 1.—Diagram representing the two divergent effects in the upper and lower extremities, and, parenthetically, the potential failure of the vasoconstrictor mechanism in the lower extremities, resulting from a common psychogenic stimulus.

That these cases do not represent functional aortic insufficiency^{5,b, 28-30} is evident from the following: (1) An aortic diastolic murmur was absent despite careful, repeated search in a quiet room. Garvin³⁰ observed aortic diastolic murmurs in all of fourteen autopsied cases of functional aortic insufficiency. (2) A brachial diastolic pressure of "0" is generally not encountered in functional aortic insufficiency. None of Garvin's cases exhibited a "0" diastolic pressure; the diastolic pressure was below 60 mm. Hg in only one of his cases (50 mm. Hg) (3) No evidence, clinical or roentgenologic, of left ventricular dilatation^{5, b} was found. (4) The diastolic pressure in the lower extremities did not reveal a corresponding change.

It is to be noted that in many instances neither the brachial systolic nor the popliteal blood pressures exhibited a complete return to normal levels on the return of the brachial diastolic pressure to readings of 60 mm. Hg or above. It is probable that this is due to the fact that the nervous influences were so pronounced that sufficiently basic levels were not attained by our relatively short rest periods. Our rest periods were directed only toward obtaining normal brachial diastolic levels. This further appears to substantiate the view that the syndrome, with its striking feature, a brachial diastolic pressure of "0," represents a marked degree of psychoneurogenic effect on the cardiovascular system. It seems possible, assuming the validity of the second hypothesis, that this same mechanism may extend to so extreme a point where the compensatory vasoconstrictor mechanisms in the lower extremities fail and a temporarily inadequate cerebral flow develops, with resultant syncope. Clinically, syncope

reactions in highly nervous examinees were not unusual. It is likely that various intermediate stages may be encountered in which the diastolic pressure in the lower extremities may exhibit subnormal values (Fig. 1).

White³¹ informs the writer that he has seen excitable persons who revealed marked peripheral vasodilatation, but he is not familiar with the circulatory responses in the lower extremities. Peripheral vasodilatation of pronounced degree is occasionally observed in hyperthyroidism^{32, 33} and hyperthyroid "crises"³⁴; apparently the lower extremities share in this response.³⁴

It is improbable that the diastolic blood pressure recorded as "0" by the indirect method represents a true 0 pressure. However, it probably does represent, in most instances, a low diastolic level. Its clinical implications, particularly in distinguishing this syndrome from true aortic insufficiency are evident.

SUMMARY

1. In the course of the routine examinations of men between the ages of 18 and 45 years of age for induction into the Armed Forces of the United States, a cardiovascular syndrome, hitherto undescribed, was observed in thirty-eight examinees exhibiting a marked degree of nervous tension.

2. In addition to the nervous element the syndrome was characterized by transient "0" diastolic brachial pressure (indirect method), normal or elevated popliteal pressure, and tachycardia.

3. The brachial systolic pressure associated with the "0" diastolic tension ranged from 118 to 250 mm. Hg and averaged 159.1. The popliteal systolic and diastolic pressures in the prone position averaged 202.3 and 101.9 mm. Hg, respectively. (In the standing position, as would be expected, the popliteal pressures were considerably higher.) The heart rate ranged from 90 to 168 and averaged 127.4. Only two examinees revealed a heart rate below 100.

4. Following rest periods varying between 5 and 90 minutes, the diastolic pressure rose to values ranging from 60 to 112 mm. Hg exhibiting an average level of 75.2. The brachial systolic pressure revealed an average fall of 11 mm Hg from the initial (prerest) levels. The popliteal systolic pressure in the prone posture exhibited an average drop of 12.5 mm. of mercury. The popliteal diastolic pressure showed an average drop of 7.1 mm. of mercury. (The popliteal blood pressure in the standing position exhibited a corresponding reduction.) The postrest heart rate ranged from 76 to 148, and averaged 104.7, representing a fall of 22.7 beats per minute.

5. The possible mechanisms involved in the genesis of the syndrome are discussed.

6. The clinical implications of this syndrome, particularly in distinguishing it from true aortic insufficiency, are evident.

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A NEW FORM OF GENERALIZED ARTERIAL DISEASE IN NEGROES

REPORT OF TWO CASES

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THAT Negroes present medical problems differing from those of Caucasians is well known. Striking examples are the racial incidence of sickle-cell anemia, the rare occurrence of typical acute myocardial infarction among Negroes, the paucity of cases of classical pernicious anemia in them, and their immunity to infectious mononucleosis. It is recognized that thromboangiitis obliterans of the Buerger's type is extremely rare among blacks.¹ We are reporting two practically identical cases of generalized vascular disease in male Negroes, the like of which we cannot find recorded in medical literature. Although the cause is unknown, the condition may properly be called a new form of generalized arterial disease, because clinically and pathologically it differs from all presently known vascular diseases. The only remotely similar form is the syndrome due to occlusion of all arteries which results from syphilitic involvement of the transverse arch of the aorta in which pulsations in the lower extremities are preserved. This syndrome has been described most recently by Aggeler, Lucia, and Thompson.²

REPORT OF CASES

CASE 1.—The patient, W. W., a male Negro, 30 years old, was admitted to Gallinger Municipal Hospital in a stuporous condition on Aug. 4, 1943. At 10:00 A.M. on Aug. 1, 1944, while still in bed and immediately after coitus, he had had a sensation of contraction in the throat followed by generalized convulsions and profuse perspiration. He was taken to a hospital, given fluid intravenously and some pills by mouth, and then allowed to return home. Another seizure of generalized convulsions developed shortly thereafter, and he vomited several times. The next morning (Aug. 2), he felt much better but became dizzy on standing and was taken to another hospital, where treatment was not given, and on the following morning (August 3) the convulsions recurred. On the morning of August 4, the patient had more severe convulsions, preceded by nausea and vomiting and followed by unconsciousness. After recovering consciousness, he noted that his left extremities were paralyzed. For a short time before the onset of unconsciousness, he had noted transient loss of vision. He stated that for three or four days before the onset of his illness he had been drinking whisky in large amounts, and he attributed his illness to the use of alcohol.

In childhood, the patient had had whooping cough and measles. In 1934 he was in an automobile accident and suffered bruises on both lower extremities and the right side of his face from the eyebrow to the chin. He was unconscious for a short time after that accident but had no disability thereafter. In 1930 he had a urethral discharge, attributed to gonorrhea, which lasted only three days and responded to treatment with "Golden Seal." In 1932 he had a penile sore and received medication intravenously and intramuscularly for a period of one year, after which he was discharged as being cured of the infection, which is thought to have been syphilis. He had been a moderately severe stutterer since childhood and was right-handed. He believed that he had been somewhat "nervous" most of his life and that this symptom had increased in severity during the several weeks prior to the onset of the present illness. For about one year he had noticed that, after a day of unusually prolonged walking, he had developed slight cramps in the left popliteal region, which disappeared shortly if he continued walking. He had no symptoms referable to other systems.

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For many years the patient had been engaged as a truck driver for a transfer company. During the past four or five years he had used about one-half pint of whisky daily but had never developed any illness which was attributed to alcohol. He had been a smoker for fifteen years, and during the past ten years he had averaged about one package of cigarettes daily. No relevant facts were elicited regarding members of his family.

The patient was a well-developed and fairly well-nourished, Negro male who lay quietly in bed without complaints. He was apparently in no distress except for mild apprehension regarding the paralysis. The temperature was 98° F., and the respiratory rate was 20 per minute. The pulse could not be palpated in any of the superficial vessels. Left hemiplegia was immediately obvious. There was very profuse perspiration on the left side of the body, whereas the skin on the right side of the body was unusually dry. The line of demarcation between moist and dry areas was quite sharp in the midline. The pupils reacted normally to light and accommodation. There was a slight or questionable degree of exophthalmos. Ophthalmoscopic examination revealed questionable papilledema; there were no hemorrhages, exudates or other abnormalities. The teeth were extensively carious. The thyroid gland was palpable and seemed to be diffusely enlarged to a slight degree. The lungs were apparently normal. Over the precordium, excessive cardiac activity was visible and palpable. The apical rate was 130 per minute. The cardiac rhythm was regular. The apex beat and left border of cardiac dullness were in the midclavicular line in the fifth intercostal space. No murmurs were audible. The aortic second sound was accentuated. All four extremities were quite cold, more so on the left than on the right. There were no palpable pulsations in the arteries of the arms, legs, or head; slight pulsations were found in the suprasternal notch, the abdominal aorta, and the external iliac arteries. Efforts to measure the blood pressure in each arm were unsuccessful when attempted by members of the resident and visiting staffs. In the lower extremities, the blood pressure was 150/120 over the left popliteal artery and 170/120 over the right popliteal artery. Examination of the neuromuscular system revealed flaccid hemiplegia on the left side with weakness of the left facial muscles. The tongue seemed to deviate to the left side on protrusion. The cremasteric and abdominal reflexes were absent on the left side. Sensation was absent on the left side, as tested by pinprick, stroking with cotton, tuning-fork vibrations, and changes in position.

Laboratory examinations during the course of hospitalization, including urinalysis, hemogram, Kahn test of the blood, blood urea nitrogen, blood cholesterol, and examinations of the spinal fluid were normal or negative. A roentgenogram of the chest was normal. Four electrocardiograms revealed only persistent elevation of the S-T segment in Lead CF₁ of about 3 millimeters. Basal metabolic rates were -15 per cent and -5 per cent. Thorotrast arteriograms of each lower extremity showed filling of the femoral arteries and a few collaterals but not of the tibial arteries. Urologic investigation was negative.

Within a few days the patient's general condition was greatly improved. There was slight fever for only two days. The paralysis rapidly improved and, after several weeks, had almost completely disappeared. Frequent examinations of the peripheral vascular system were made independently by numerous observers. A tabulation of the results of these examinations shows remarkable agreement. The last observation was made on Feb. 24, 1944, after the patient had left the hospital. All examiners stated that there were no pulsations in the arteries of the right side of the head, neck, and the right upper and lower extremities. On only one occasion was the left temporal artery said to be pulsating. The left external maxillary artery was never found to pulsate. The left common carotid was thought to pulsate weakly only on the last examination. The left subclavian and axillary arteries were thought to be pulsating, each on only one occasion. The left brachial artery was thought to pulsate weakly less than half of the time. The left radial was not palpable on most occasions but was well felt on the last. The left ulnar artery was felt to pulsate on the last examination only. The abdominal aorta had strong pulsations throughout. The right external iliac was said to have weak pulsations at first and strong ones later. Pulsation in the right upper femoral artery was felt on a few occasions only and then was said to be weak. The right popliteal artery was felt only once, while the right dorsalis pedis artery was never felt. The right posterior tibial artery in the foot was felt to pulsate from Oct. 19, 1943, on, and was considered to be pulsating normally before the patient left the hospital. The left external iliac artery was pulsating weakly at first, but normally later, whereas the left femoral arterial pulsation, at first imperceptible, later became feebly palpable. The left popliteal artery was thought to be pulsating feebly on one occasion, but the left dorsalis pedis artery was never felt. Pulsations in the left posterior tibial artery were not felt until Oct. 19, 1944, and then appeared, increasing gradually to normal strength.

The blood pressure could not be measured in the right arm until Nov. 4, 1943, and was then recorded at a low level, finally attaining 86/76. In the left arm there was no measurable blood pressure at first, but it became evident at a low level on Sept. 9, 1943, and finally reached 112/98. In the right thigh (popliteal artery) the blood pressure ranged from 158 to 230 systolic and from 90 to 140 diastolic; the last measurement was 190/102. In the left thigh the pressure ranged from 148 to 200 systolic and from 90 to 120 diastolic, the last recording being 180/100. On one occasion 0.03 Gm. of papaverine and, on another, 2 c.c. of Spas malgin, given hypodermically, did not alter the pulsations or the blood pressure measurements. Oscillometric examinations confirmed these findings.

There were no trophic changes in the extremities; both feet remained equally cool. When last seen, the patient had a very slight residual limp, but other evidences of the paralysis had practically disappeared. His weight had increased from 136 pounds to 151 pounds.

On Aug. 25, 1943, a segment of the right radial artery was removed for histologic examination. There was no bleeding from the artery and only slight bleeding from the veins. Histologic sections of the artery showed a small, star-shaped lumen. There was no evidence of active inflammation (Fig. 1). The intima was not thickened. The media (demonstrated with Mallory's connective tissue stain) had suffered disappearance of most of the muscle fibers with replacement by fibroblasts. Sections stained with Weigert's elastic tissue stain revealed the internal elastic lamina to be somewhat broadened and thickened, with practically no elastic fibers in the media. The adventitia was not altered, and the veins appeared to be normal.

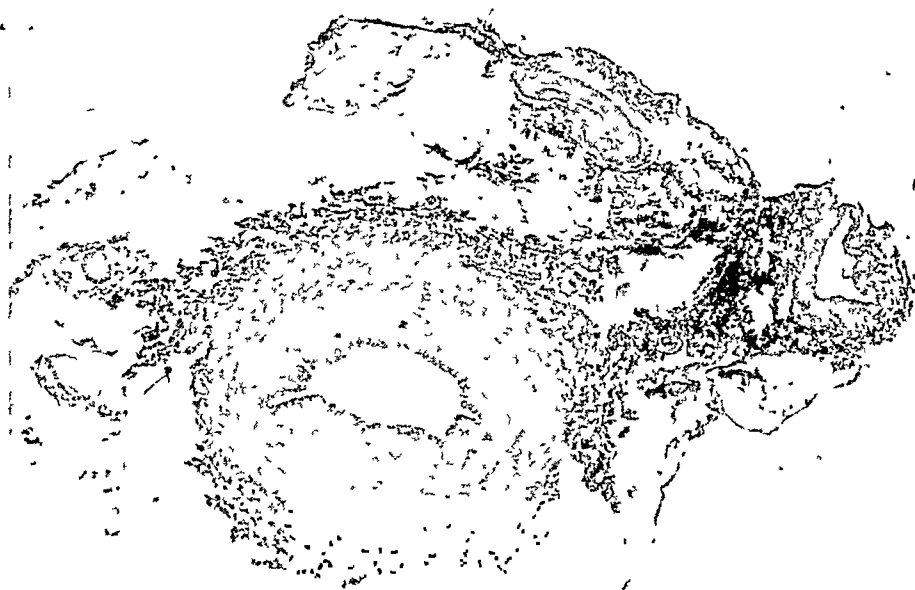


Fig. 1.—Case 1. Cross section of radial artery. Fibrosis of media. Reduced from a magnification of $\times 30$. (Photograph from Army Medical Museum, Washington, D. C.)

CASE 2.—The patient, K. B., a male Negro, 30 years old, was admitted to Gallinger Municipal Hospital at 5:20 P.M. on Dec. 24, 1943. Shortly after awakening at 7:30 A.M., he had developed a severe headache in the right temporal and parietal regions. Within a few minutes he became completely blind in the right eye, and the left upper and lower extremities became paralyzed. Consciousness was lost about 8 A.M., and he was found by members of his family several hours later. During the night before, he had drunk a pint and a half of cheap whisky and had become nauseated, but not intoxicated.

For about a year and a half, the patient had had aching pain in the calves of the legs after walking or running a short distance. Usually the pain began after he had walked one or two blocks and gradually increased, if walking was continued. The pain was more severe in the right calf than in the left. During this time he was employed as a bellboy in a hotel and was able to do his work only because he made short trips. At the same time he had slight impairment of vision in both eyes, but this was not severe enough to prevent his driving an automobile. He had had mild headaches for a long time, and these had been more frequent and more severe during the three weeks prior to the onset of paralysis. There had also been

mild dizzy spells, usually more severe after bending over. In childhood he had had mumps, whooping cough, measles, chicken pox, and scarlet fever. At preschool age there had been an illness of unknown nature followed by slight permanent weakness of the left facial muscles. Pneumonia had occurred in 1940. The patient had had gonorrhea twice, the second time in 1941, but there was no history of syphilis. Tonsillectomy had been performed in 1943 because of frequent sore throat, which did not recur following operation. A pint of whisky had been used daily for a year, about one year before the present illness.

On admission to the hospital the patient was stuporous and somewhat combative when aroused. There was urinary incontinence. He was well developed and well nourished. Complete paralysis of the left side of the body, including the lower half of the face, was obvious, but the deep reflexes were slightly increased on both sides, perhaps a little more on the left. The abdominal reflexes were absent; the cremasteric was absent on the left and present on the right. Babinski's sign was prominently positive on the left and negative on the right. The circumference of the left thigh was 6 cm. less than that of the right. The rectal temperature was 99° F., and the respiratory rate was 20 per minute. Of unusual interest was the absence of pulsations in all peripheral arteries except in the left arm, the femoral arteries in Scarpa's triangle, and possibly the left carotid. There was great tenderness over the right carotid artery, which persisted for at least six weeks. The pulse rate was 80 per minute in the left arm; the blood pressure measured 140/100. Ophthalmoscopic examination revealed pallor of the right optic disc and severe narrowing of the arterioles; the left fundus appeared to be normal. Laboratory tests, including urinalysis, blood counts, blood Kahn test, blood urea nitrogen, blood cholesterol, basal metabolic rate, and examination of the spinal fluid were all normal or negative. Electrocardiograms made on January 21 and February 10 revealed only that the P-R interval was 0.2 to 0.22 second. Urologic investigation was negative.

The status of the patient did not change much during the first week. In the second week the sensorium cleared progressively. During these two weeks the rectal temperature ranged daily between 100° F. and 101° F. By the fourth week the patient was able to stand, and by the sixth week he was able to use his arm and leg to about 50 per cent of normal capacity. At this writing, Oct. 28, 1944, there is still a limp, some clumsiness of the left hand, and almost complete paralysis of the lower half of the left side of the face. There is complete right optic atrophy. The reflexes are normal.

During these ten months of observation, the peripheral vascular system was examined repeatedly by numerous physicians. A tabulation of these examinations reveals that the right temporal artery was found to be pulseless except on two or three occasions when it was thought to have a faint pulsation; the right carotid artery was always pulseless, as was the right external maxillary; the right subclavian artery was pulseless except during the last two months; the right axillary artery was pulseless until now, the time of writing, when it appeared to pulsate normally; and the right brachial, radial, and ulnar arteries were continuously pulseless. Pulsations of the right femoral artery were recorded as varying from absent to normal, but were usually present; but the right popliteal, dorsalis pedis, and posterior tibial arteries were always pulseless. On the left side the temporal artery was usually recorded as pulseless, the carotid pulsation as absent or weak, the external maxillary as absent or weak, the subclavian from absent to normal, and the axillary, brachial, radial, and ulnar pulsations were usually normal, although recently weaker. The pulsations of the left femoral artery were recorded as being absent, weak, palpable, normal, or strong, but definitely present; the left popliteal artery was recorded to have pulsations ranging from absent to strong but recently weak, and the same statement applies to pulsations of the left dorsalis pedis and posterior tibial arteries, which are now very weak. Oscillometric examinations corresponded with these results.

Blood pressure measurements were obtainable only in the left arm and the left thigh. In the former, they were usually about 130/90; whereas in the left thigh (popliteal region) they were not obtainable until April, since when they have varied from 150 to 215, systolic, and 100 to 160, diastolic. On the last examination the reading was 155/100. On April 13, 1944, following the intravenous injection of 60 mg. of papaverine, there was no appreciable change in the degree of any arterial pulsation or in the blood pressure readings.

There have been no trophic changes of the extremities or digits. The feet have been relatively cold. At first, the right was cooler than the left, but recently the left foot has become considerably cooler than the right.

On Jan. 11, 1944, an arteriogram of the right leg, obtained by injecting Thorotrast into the right femoral artery in Scarpa's triangle, failed to show filling of the arteries below the middle of the thigh. On April 4, 1944, a left carotid arteriogram, made by injecting the Thorotrast directly into the common carotid artery through the skin, showed filling of all

cerebral vessels of the left hemisphere but none of the right. This test was repeated on Oct. 11, 1944, after surgical exposure of the artery, and revealed the same condition. On direct examination during operation the artery appeared to be much thicker than normal.

On Jan. 1, 1944, a biopsy was made of the left posterior tibial artery. Both vein and artery were of small diameter. The vein was patent, but the lumen of the artery was very small; both were bloodless. On Oct. 18, 1944, Dr. J. Ross Veal exposed the right common carotid artery and found it pulseless and solid. The veins were patent, and there were no adhesions around the vessels. A segment of the artery was excised without the need for ligation. Sections of the posterior tibial artery showed the vessel to be thickened and the lumen slitlike (Fig. 2). The intima was slightly thickened. The media was interspersed with fibrous tissue which had replaced about 60 per cent of the muscle fibers. The internal elastic lamina was moderately thickened. The adventitia appeared to be normal. There were no active inflammatory elements. The veins were apparently unaffected.

Examination of sections of the right carotid artery show the lumen to be eccentric and reduced to about one-third normal size and filled with an unorganized clot (Fig. 3). The remainder of the old lumen was filled with organized tissue which may have been the result of subintimal proliferation. All of the blood vessels in this tissue were small endothelium-



Fig. 2.—Case 2. Cross section of dorsalis pedis artery with vena comitantes. Slitlike lumen with severe fibrosis of media of artery. Reduced from a magnification of $\times 30$. (Photograph from Army Medical Museum, Washington, D. C.)

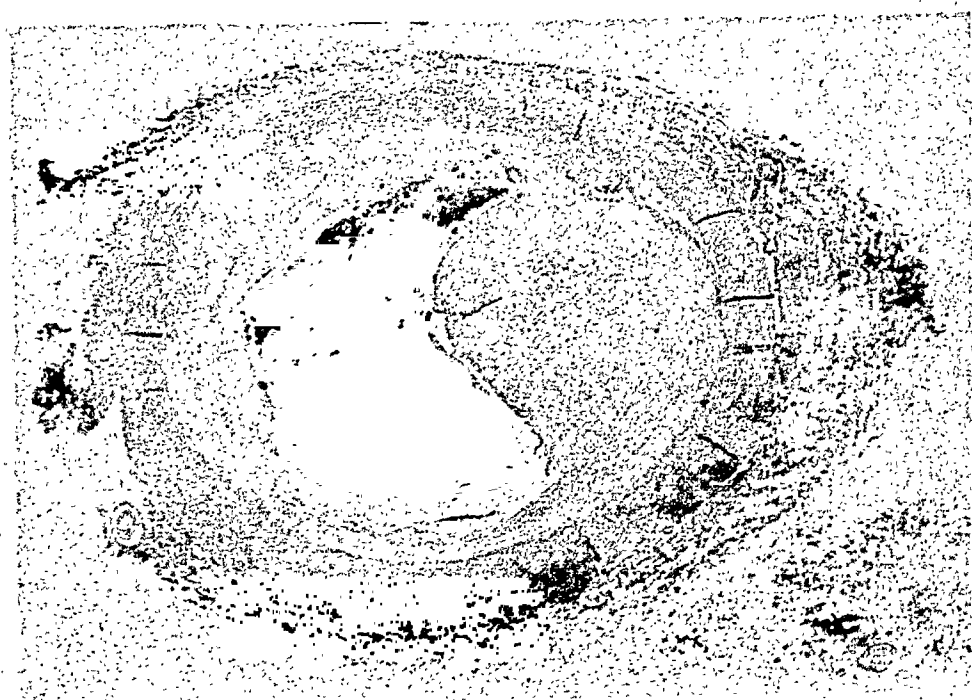


Fig. 3.—Case 2. Cross section of right common carotid artery. Subintimal proliferation with reduction of size of lumen, which is filled with unorganized clot. Reduced from a magnification of $\times 15$. (Photograph from Army Medical Museum, Washington, D. C.)

lined spaces. This tissue looked like a network with irregularly sized, rounded spaces interspersed with darkly staining nuclei. Some of the spaces appeared to have contained cholesterol, but a stain for fat was not made before embedding. The presence of mucin was ruled out by means of a mucicarmine stain. The spaces were probably, therefore, the result of edema. The media had been replaced largely by connective tissue, most notably in the inner half (Fig. 4), as shown by Brilmeyer's stain. Sections stained with Weigert's elastic tissue stain showed a moderately disrupted internal elastic lamina, and the elastic fibers of the media seemed to be denser than normal, but this effect might be due to narrowing of the

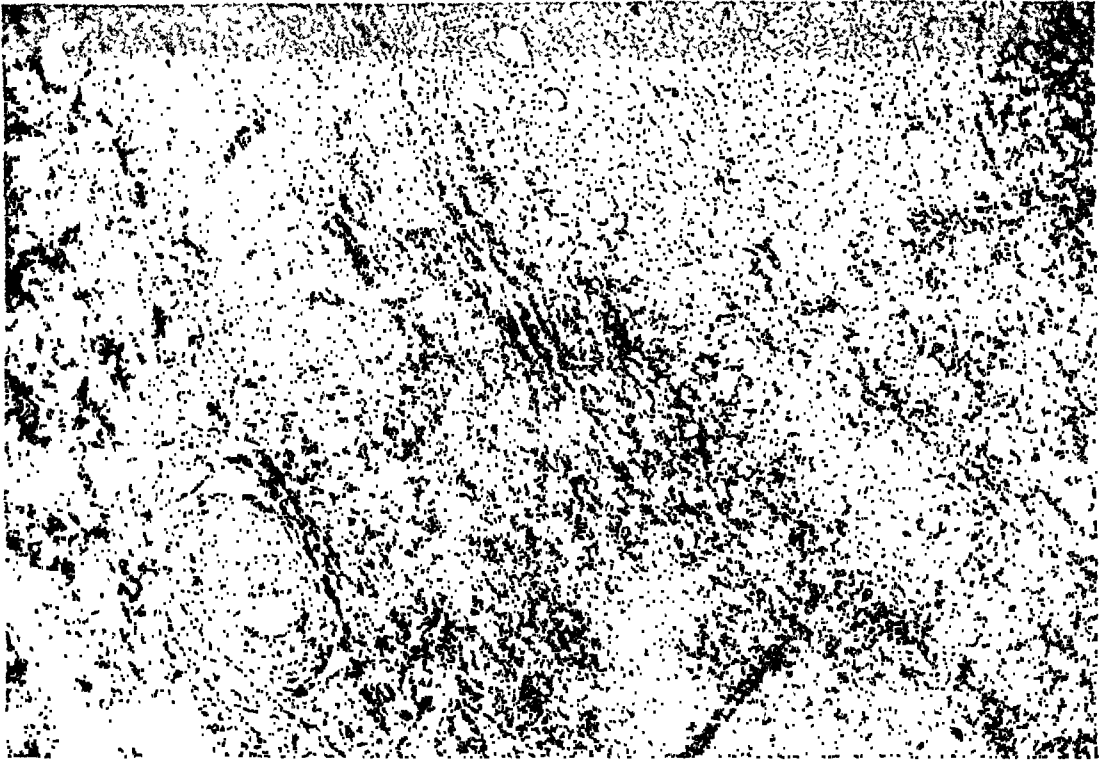


Fig. 4.—Case 2. Fibrosis of media and subintimal proliferation of right common carotid artery; small artery in adventitia on left, with small lumen and subintimal proliferation. Reduced from a magnification of $\times 100$. (Photograph from Army Medical Museum, Washington, D. C.)

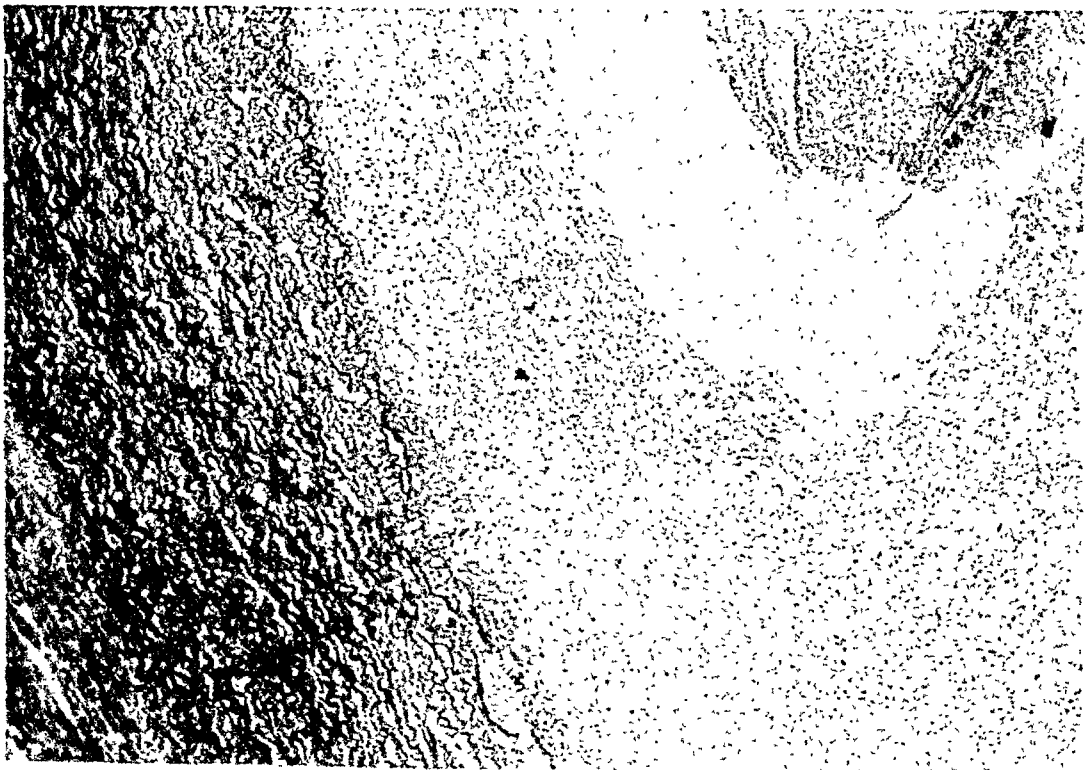


Fig. 5.—Case 2. Elastic tissue stain of right common carotid artery: media and subintimal proliferation shown. Reduced from a magnification of $\times 100$. (Photograph from Army Medical Museum, Washington, D. C.)

media from contracture (Fig. 5). The small arteries in the adventitia had small lumens and greatly thickened walls due to marked subintimal proliferation, and there was great reduction in the thickness of the media. Nowhere was there any evidence of inflammation.

DISCUSSION

The only vascular disease of known cause is that due to syphilis. So far as our definite knowledge is concerned, the only vessels of the body affected by syphilis are the aorta and other large arteries and the small arteries of the central nervous system. Cases of disease of the medium-sized arteries, particularly of the extremities, have been reported as being caused by syphilis, but the proof is inadequate. Because syphilis is so prevalent among Negroes, it is not unnatural to try to attribute arterial disease in members of this race to this cause, when a definite etiological diagnosis cannot be made. Although one of our two patients had had syphilis, there is no histologic or other evidence that the vascular disease is of that origin. Neither patient had evidence of aortitis or of syphilitic disease of the central nervous system, and Kahn tests on both were negative.

In 1937, one of us (W. M. Y.)¹ reported five cases of thromboangiitis obliterans in male Negroes. The lower extremities were mainly affected. On the whole, the findings in these cases closely resembled those of Buerger's disease in Caucasians. One of us (W. M. Y.) has not observed any more cases of vascular disease resembling Buerger's disease among Negroes, but an additional patient with this condition has been treated in this institution by Dr. J. Ross Veal. Two of the five patients reported have remained under observation. One (Case 1) has not had any further symptoms referable to his feet, which he has excellently cared for. He is now suffering from chronic congestive heart failure, the result of calcific aortic stenosis and regurgitation. The other patient (Case 4) has had no further symptoms except for an attack of acute superficial phlebitis which responded promptly to treatment. All five of the patients had or had had syphilis, but biopsies of their arteries did not reveal evidence of that disease.

These two new cases of unusual vascular disease in male Negroes cannot be explained, but it is our opinion that there have been multiple silent episodes of thrombosis in medium-sized, and even larger, arteries, mainly of the peripheral vascular tree. The first symptom was the onset of intermittent claudication and this was followed, more dramatically, by thrombosis in an artery serving the brain. That this thrombosis might have been the result of acute arteritis was suggested by the extreme tenderness over the right carotid artery in Case 2, but histologic examination of the artery ten months later did not reveal any residual inflammation, which might have been expected to persist. It was baffling and astounding to all observers to see two patients without pulsations in practically all of the peripheral arteries, a phenomenon which none had previously seen in living subjects not in a state of extreme shock.

The study of the biopsy specimens in the two cases did not help to elucidate the nature of the disease. That the arteries were occluded proximal to the area of biopsy was shown by the lack of bleeding when the sections of the arteries were excised. The fibrosis of the media and the small size of the lumen could have been the result of disuse alone. That the lack of pulsations in so many arteries was not due to spasm was demonstrated by the fact that antispasmodics did not produce any change and that, as the months passed, there was very moderate improvement in the amplitude of pulsations. The collateral circulation was adequate, as attested by the absence of trophic changes, except following the cerebral episodes which left slight residual defects.

In the sections of arteries examined there was no evidence of active inflammation. The fibrosis was confined to the media, and there was no indication of previous periarterial inflammation. The carotid artery in Case 2, examined by biopsy ten months after the development of the hemiplegia, showed irregular and extreme subendothelial proliferation and some disruption of the internal elastic lamina. Strangely, the clot in the narrowed and irregular lumen showed no organization. The small arteries surrounding the carotid also showed subintimal proliferation and reduction in size of the lumen.

The absence of inflammatory elements in the biopsy specimens leads us to suggest the possibility of some chronic intoxication that lead to degenerative changes of the intima at certain points, with resultant subintimal proliferation and, eventually, thrombosis. That "essential thrombophilia," as described by Nygaard and Brown,³ was not the cause of the thromboses is shown by the absence of venous thromboses. The disturbance in our two patients is distinctly arterial.

The findings in the two cases showed no similarity to periarteritis nodosa.^{4, 5} They are certainly not similar to those of generalized thromboangiitis obliterans of the Buerger's type, either clinically or histologically. The cerebral vascular accidents were undoubtedly the result of thrombosis of the common carotid artery (Case 2) and of either the common carotid or the internal carotid arteries (Case 1). In cases reported as cerebral thromboangiitis obliterans, cerebral vascular phenomena have apparently been the result of widespread involvement of the small vessels in the brain,⁶ rather than in the larger arteries, and inflammatory elements have been present.

SUMMARY

Two cases of a previously undescribed form of arterial disease have been reported. Both patients were male Negroes, 30 years of age, who were well except for recent intermittent claudication, until affected by hemiplegia of sudden onset. Pulsations were absent in practically all of the peripheral arteries except the upper femorals, and in greatly reduced intensity in a few others. A striking feature was the absence, or great impairment, of pulsation in the arteries of the neck and head. The nature of the disease could not be ascertained. It is postulated that an arterial degeneration of unknown cause resulted in multiple thrombotic episodes in numerous portions of the peripheral vascular tree, including those of the head and neck.

The photomicrographs used herewith were made by Mr. Roy M. Reeve, Army Medical Museum, Washington, D. C., negatives numbered 83944 through 83948.

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THE EVALUATION OF VASCULAR RESERVE IN PERIPHERAL VASCULAR DISEASE

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ALTHOUGH clinicians in the past were well acquainted with the symptoms and signs of peripheral vascular disease, it was not until the last two decades that methods were described to test the patency of the blood vessels of extremities. In 1926, Brown¹ obtained vasodilatation by means of intravenous administration of typhoid vaccine. In May, 1930, White² and Brill and Lawrence,³ at the same time, but working independently, showed that spinal anesthesia caused an increase in the surface temperature of the feet. Scott and Morton,⁴ in June, 1930, found that general anesthesia gave the same complete abolition of vasoconstriction. Again, in October, 1931, Scott and Morton⁵ injected the posterior tibial nerve to differentiate arterial spasm from organic obstruction. Sir Thomas Lewis,⁶ in 1929, used heat to induce peripheral vasodilatation, and, in 1932, Gibbon and Landis⁷ produced a similar reflex result in the legs by immersion of the forearms in warm water. The latter authors decided, in 1933,⁸ that the immersion test compared favorably with the other methods of vasodilatation. In 1938, Beck and deTakats⁹ injected sodium nitrite intravenously and observed the increase in oscillations, as measured by the oscillogometer.

When one who works with peripheral vascular disease is presented with such a variety of procedures, he is really at a loss to know which method he should use, from the point of view of ease of procedure and dependability of result. It is not very feasible, of course, to give a patient spinal or general anesthesia for the testing of vasodilatation, especially as a clinic or office procedure. For the past eight years, therefore, we have experimented with the various methods of producing vasodilatation, and the details of these findings may be found in other publications.^{10, 11} The final conclusion from all these studies was that novocain block of the common peroneal and posterior tibial nerves was the test of last appeal to determine whether full vasodilatation could be obtained, and the measure of the degree of vasodilatation was designated as vascular reserve.

Due to the fact that many who work with peripheral vascular disease block only the posterior tibial nerve and omit the common peroneal, it was felt that we should determine to our satisfaction whether or not that procedure alone was sufficient to give full vasodilatation. We desired to find out if it was necessary to include the common peroneal or if blocking the common peroneal was a superfluous procedure.

PROCEDURE

We chose twenty patients in whom full vasodilatation had been obtained by blocking both the common peroneal and posterior tibial nerves with 2 per cent novocain without adrenalin. The diagnoses in these cases were as follows: arteriosclerosis obliterans, eight; no peripheral vascular disease, six; post-phlebotic syndrome, two; vasospasm, two; scleroderma, one; thromboangiitis obliterans, one.

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After full vasodilatation had been shown, block was produced in each patient at two subsequent visits to the clinic; at one time the posterior tibial nerve alone was blocked, and on the other visit the common peroneal nerve was injected. No readings were considered valid unless the nerve block had been definitely confirmed as follows: Block of the common peroneal nerve was indicated by (1) loss or diminution of sensation of the entire dorsum of the foot, or (2) inability to flex dorsally the toes of the foot, inability to flex dorsally the foot on the ankle, and inability to evert or invert the foot. Block of the posterior tibial nerve was demonstrated by loss or diminution of sensation on the plantar aspect of the foot. The common peroneal nerve was blocked at the neck of the fibula, and the posterior tibial nerve was blocked 1 inch above the lower end of the internal malleolus on the posterior aspect.

All tests were carried out with the room temperature below 26°C .; it was often as low as 19°C . and once went as low as 16.1°C . Block was not attempted unless the temperature of the large toe, to be tested, was below 26°C . Often the toe temperature was nearer 20°C . Full vasodilatation was indicated by a temperature of at least 30°C . one hour after confirmation of the block. All readings were made at the base of the nail of the large toe, and were taken with the Taylor dermatherm. The results were estimated in percentage rise from the starting temperature below 26°C ., to 30°C . For instance, if the temperature on the large toe before the block was 20°C ., a rise to 30°C . represented 100 per cent vasodilatation; likewise, a rise at the end of one hour to only 28°C . represented eight-tenths or 80 per cent vasodilatation. Only one case was included that showed a rise to only 29.5°C . after blocking both nerves.

RESULTS

Blocking of both the common peroneal and posterior tibial nerves. All patients showed a rise from below 26°C . to at least 30°C ., except the one mentioned above which showed a rise to only 29.5°C .

Block of the posterior tibial nerve only. Eleven of the twenty patients showed a rise to 100 per cent; one showed no rise at all; and the other eight showed increases of 56, 60, 75, 80, 80, 85, 87 and 91 per cent, respectively.

Block of the common peroneal nerve only. The data in three cases were not recorded; three patients showed no rise at all; and the others showed increases of 8, 23, 27, 27, 33, 40, 50, 59, 63, 71, 80, 82, 86, and 100 per cent, respectively.

COMMENTS

In May, 1940, we published criteria for the classification and diagnosis of peripheral vascular diseases.¹² At that time we emphasized the point, that it was important in reporting results of therapy, that the initial status of the patient be determined, that some method be established to determine progress, and that uniform diagnostic standards be established to make possible valid comparisons of data from many sources and to permit crystallization of prognostic and therapeutic principles from these data.

We also felt, as we do now, that determination of vascular reserve is the most important single objective in the study of the patient. It is a measure of degree of vascular impairment and an indication of how much we may hope to attain with suitable therapy. Periodic determination of vascular reserve is useful also as a means of following changes in the vascular status of the patients' limbs. The only known way to determine this vascular reserve is by vasodilatation tests,

and the only methods that give the answer unequivocally are those that eliminate the vasoconstrictor pathways. These methods in the past have proved to be paravertebral block, sympathectomy, spinal or general anesthesia, and peripheral nerve block; and, as has been shown in this communication, in the case of peripheral nerve block, one must employ block of both the common peroneal and the posterior tibial nerves simultaneously.

CONCLUSION

Twenty patients, in whom novocain block of the common peroneal and posterior tibial nerves produced complete vasodilatation, were tested subsequently by blocking the common peroneal and posterior tibial nerves individually at different times. It has been shown that, while block of the posterior tibial nerve alone gives more efficient vasodilatation than block of the common peroneal alone, one must block both nerves simultaneously in order to get a dependable and unequivocal result. Block of either one of these nerves alone cannot be relied on to give the maximum vasodilatation at all times.

We wish to give credit to Mrs. Rosa Abraham, R.N., and Mrs. Leah Banks for their valuable technical assistance.

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Clinical Reports

ELECTROCARDIOGRAMS SIMULATING POSTERIOR MYOCARDIAL INFARCTION AFTER CESSATION OF PAROXYSMAL TACHYCARDIA

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THE purpose of this paper is to report another cause for abnormal S-T and T changes other than myocardial infarction. Geiger¹ reported such a case in a recent issue of THE AMERICAN HEART JOURNAL. I wish to add this case to the literature.

CASE REPORT

O. C., a 62-year-old farmer, registered in the Clinic on Nov. 3, 1942. His chief complaint was "heart attacks." These consisted of an exceedingly rapid heart rate associated with nausea and vomiting. His heart attacks began five years previously. At that time he would go for many months without having an attack, but later they were more frequent. Some of the attacks lasted only a minute, but some continued as long as eight hours. The onset and cessation of the attacks were instantaneous. Previous to his last attack, he would be able to resume his duties as soon as his heart returned to a normal rate. His last attack occurred six days prior to registration. With most of these seizures he would have a choking sensation and pain in the neck. With the most severe attacks he would suffer nausea and vomiting. The last attack also was associated with severe epigastric pain. This had disabled him so that he felt weak, lightheaded, and staggering. It was the patient's thought that certain foods, such as apples and other fruits, might bring on an attack. He had to take a laxative twice a week. His systemic history was otherwise negative except for rheumatism that had existed for twenty-five years. His family history was negative except that his father died at 80 with gangrene of the foot. His marital history was negative.

Physical examination revealed a man 66 inches tall and 221½ pounds in weight. The blood pressure was 145/88 in both arms; the pulse was 58; and the temperature was 97.6° F. His teeth were deserving of x-ray study. The nasal mucosa was of the chronic catarrhal type. The tonsils were normal. The heart and lungs were normal physically. There was tenderness over the spine, left costovertebral area, and right costal margin.

Because paroxysmal auricular tachycardia and rheumatism may be associated with foci of infection, numerous laboratory studies were done. Complete blood counts, blood Mazzini, and blood sugar were normal. The blood uric acid was 4.1 milligrams. The urinalysis, gastric analysis, and basal metabolic rate were normal. Although his prostatic secretion revealed no pus cells, the dextrose brain broth culture produced a streptococcus. The stool culture was negative. The electrocardiogram was normal (Fig. 1). The chest film revealed a normal cardiac silhouette and normal lung fields. Intravenous pyelograms were normal but marked arthritic changes could be seen in both hip joints and lumbar spine. Cystoscopic examination was negative except for slight prostatic enlargement and a small stricture in the membranous urethra. A gastrointestinal series and barium enema were normal except for hypertonicity. Cholecystograms were normal. Dental rays revealed periapical infection on number 23 and pyorrhea, Grade 4, on the lower anterior teeth.

Our diagnosis was paroxysmal auricular tachycardia in an otherwise normal heart. He also had an abscessed tooth and pyorrhea with osteoarthritis.

The patient wasn't seen again until the morning of Nov. 25, 1942. Two nights previous to admission he suffered another attack of tachycardia. This was associated with pain in the neck and a choking sensation. He was in a state of shock. His lips and fingernails were blue. The radial pulse was imperceptible, but the apex beat was 220. The blood pressure was 50/40. There were râles in both lung bases.

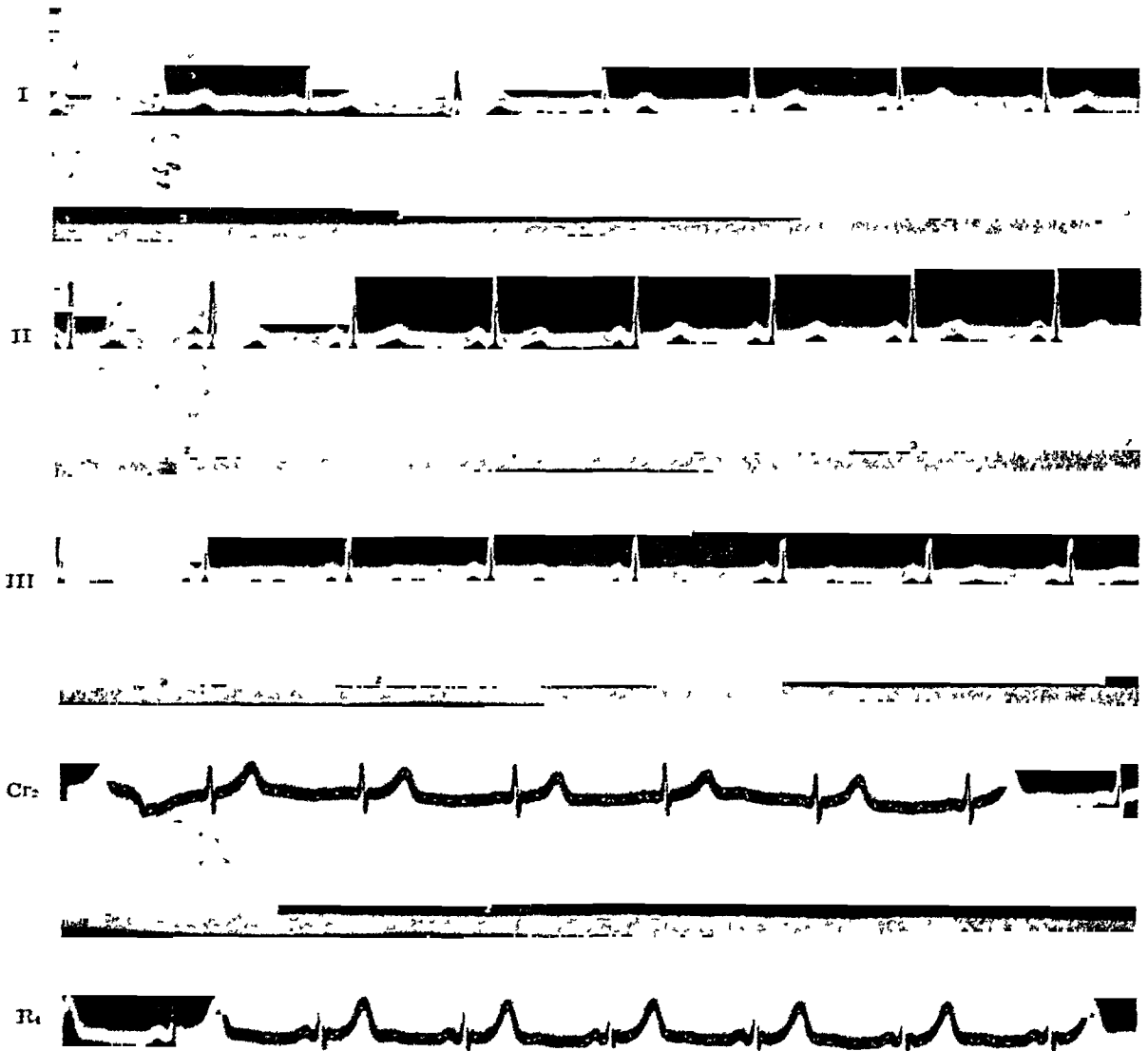


Fig. 1.—Electrocardiogram taken when patient was first seen on Nov. 11, 1942.

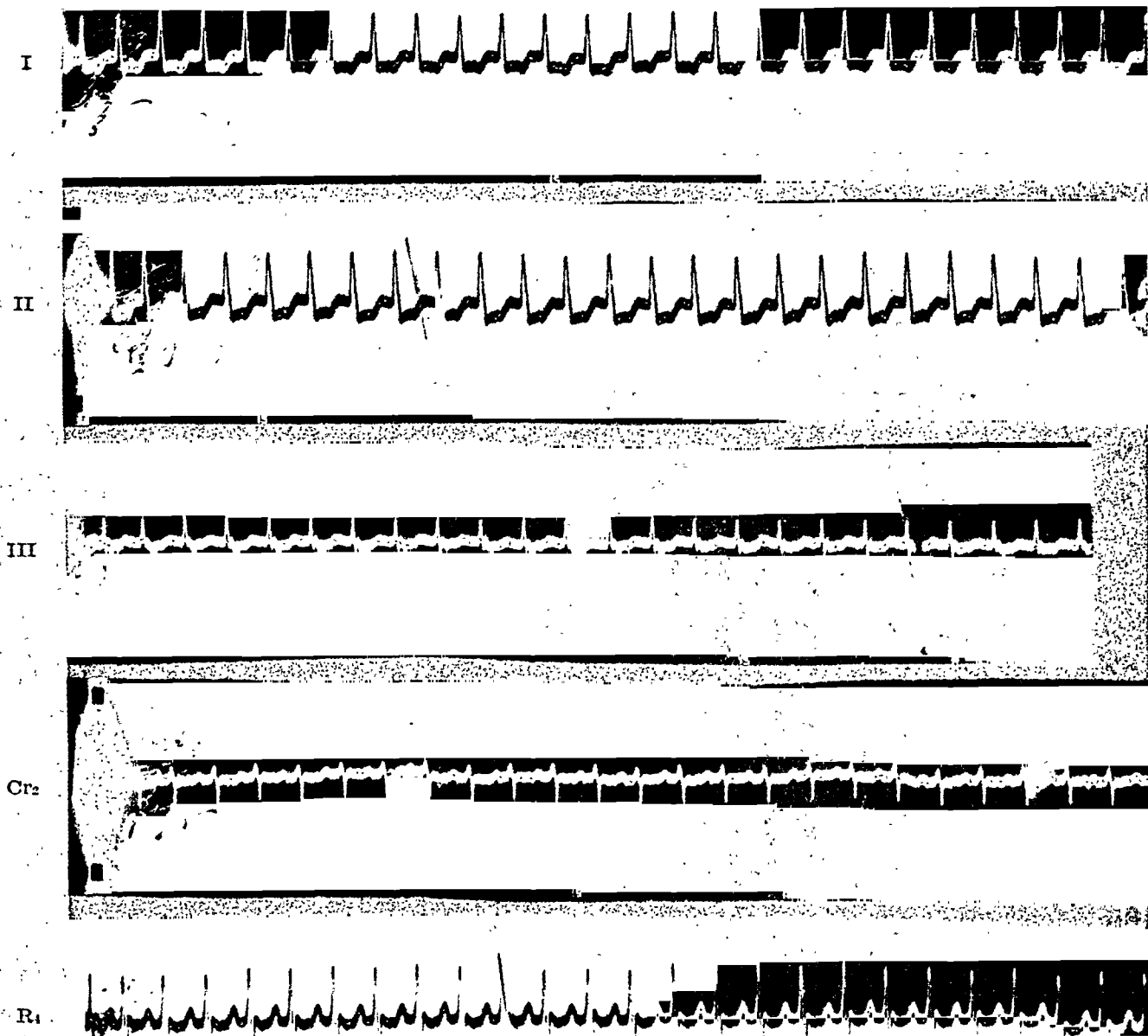


Fig. 2A.—Electrocardiogram taken when patient returned on Nov. 25, 1942, sixty hours after onset of an attack of paroxysmal auricular tachycardia. Note S-T depression and effects on T waves.



Fig. 2B.—Electrocardiogram taken on Nov. 28, 1942, showed T changes suggesting myocardial infarction.



Fig. 2C.—Electrocardiogram taken on Dec. 4, 1942. By now the digitalis effect was worn off and T_1 is upright but $T_{2,3}$ and CR_4 are still inverted.

The electrocardiogram showed a rate of 220 with S-T depression and corresponding T changes in all leads (Fig. 2A). Neither ocular pressure nor carotid sinus pressure helped. At 8:30 p.m. the radial pulse and blood pressure were not obtainable. The apex beat was 220 per minute. However, his color was improved due to the inhalation of 100 per cent oxygen by mask. One hour later since there was no change for the better, 5 c.c. Digiglusin were given intravenously. By 1:30 a.m., Nov. 26, 1942 (four hours later), the radial pulse was regular at 88 beats per minute. By 8:30 a.m., the pulse was 74, the blood pressure was 115/85, and the color was pink. On Nov. 28, 1942, the electrocardiogram showed a rate of 70 with a normal sinus rhythm. T_1 tended to be diphasic but T_2 and T_3 were inverted and CR_4 was diphasic. (See Fig. 2 to note progressive improvement and return to normal within two months' time.)

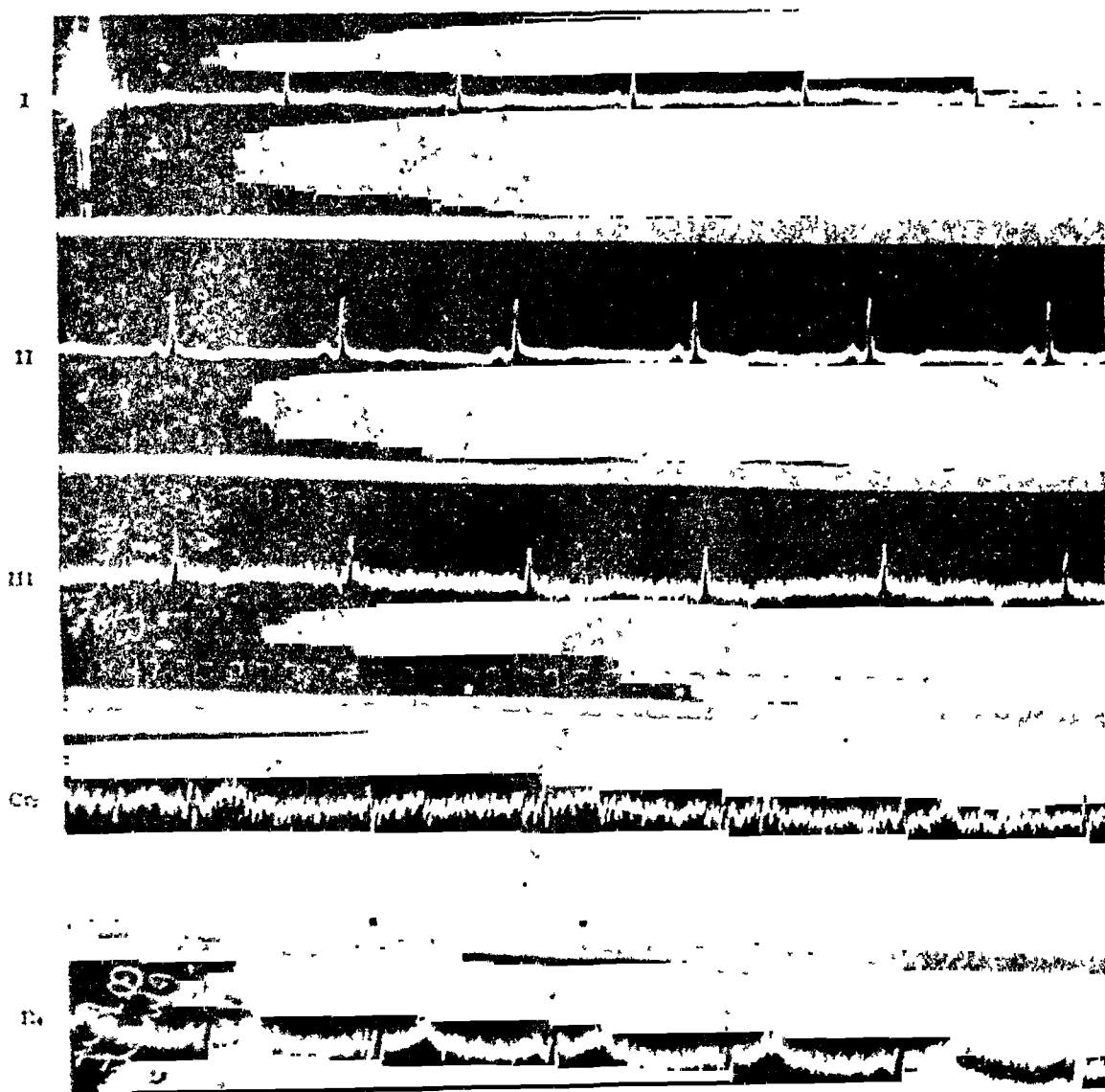


Fig. 2D.—On Dec. 10, 1942, T_2 and T_3 were inverted but CR_4 was upright.

The patient remained hospitalized until Dec. 18, 1942, because it was thought he had a coronary occlusion. His treatment consisted of continued rest, aminophylline, a nerve sedative, and quinine. It was hoped that this would prevent another attack.

He returned for examination on Jan. 29, 1943. He had suffered no symptoms from his heart, but his rheumatism was worse. His blood pressure was 170/100, but his electrocardiogram had returned to normal (Fig. 2F).

The patient was not seen again until Feb. 10, 1943. He was doing nicely until two nights before admission when a similar type of heart attack was encountered. The patient was very pale and cyanotic. He was listless but had an apprehensive

look. The pulse rate was 200, and the blood pressure 75/60. The electrocardiogram (Fig. 3*A*) showed an A-V rate of 200. Notching is present in all QRS complexes. There is depression of the S-T segment with diphasic T waves in all leads.

Five cubic centimeters of digiglusin were given immediately and oxygen was started. Twelve hours later the pulse was still 200, so 3 c.c. more of digiglusin were given intravenously. It was two days later before the pulse returned to a normal level. A total of 10 c.c. of digiglusin were required this time to produce a normal sinus rhythm. (See Fig. 3*B* for the electrocardiographic changes.) This attack was quite shocking to the patient, and it seemed to take several days for him to regain his strength. Within ten days he was feeling quite well, and we permitted him to leave the hospital in two weeks.

We now felt that these T changes were functional in origin as a result of the paroxysmal auricular tachycardia.

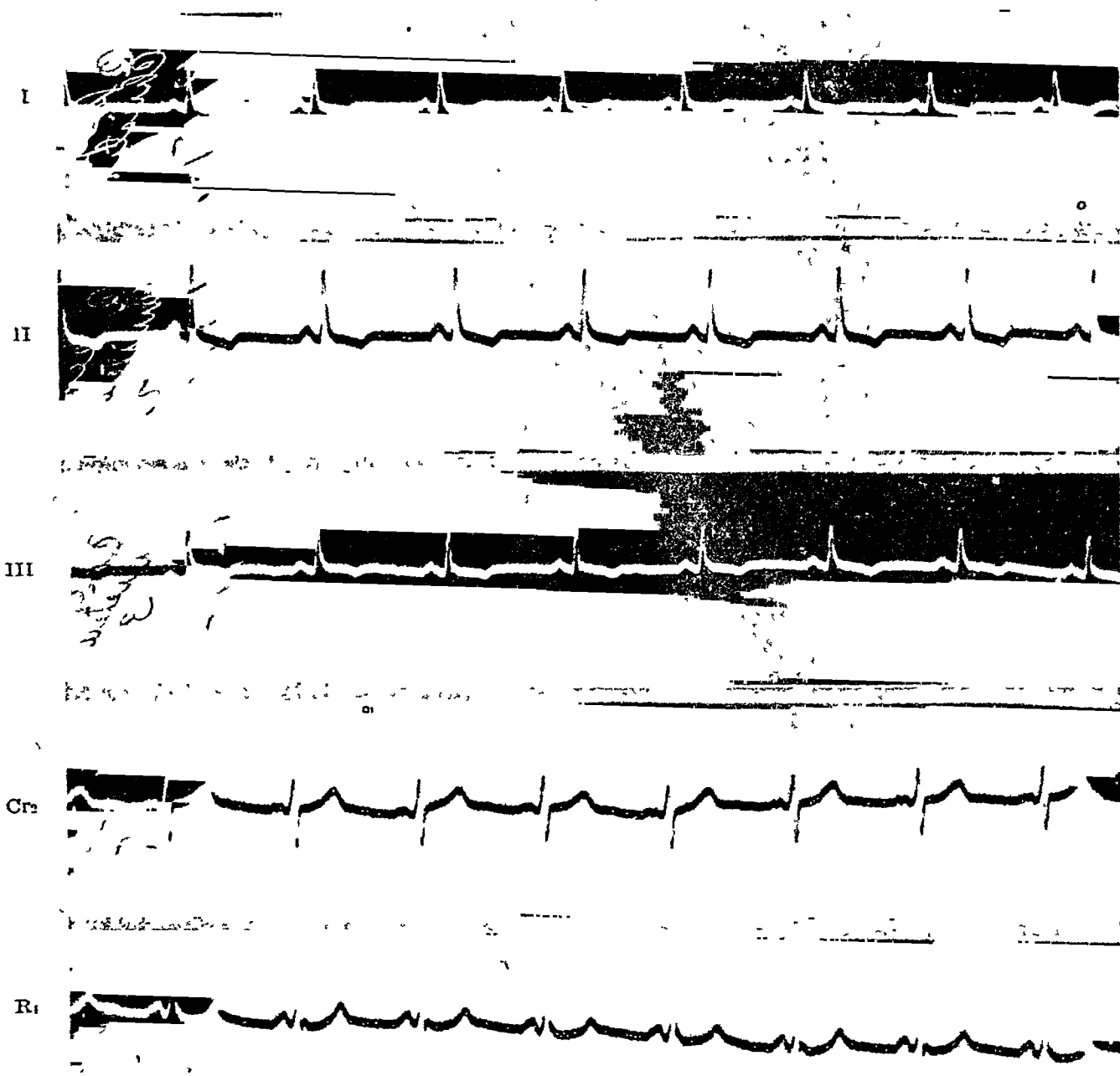


Fig. 2*E*.—On Dec. 18, 1942, the T waves were inverted in all of the standard leads but CR₁ was still upright. Why T₁ is inverted in this tracing is unexplained.

DISCUSSION

As Geiger¹ pointed out, it is very important to differentiate this type of T change due to functional disorder from that due to a coronary occlusion.

The most common age for paroxysmal auricular tachycardia to occur is between 20 and 30 years, but in this case the patient was 62 years, an age at which coronary occlusion commonly occurs. All clinical and laboratory evidence favored a normal heart except those electrocardiographic changes immediately following the attacks. It is of importance to note that the patient was first

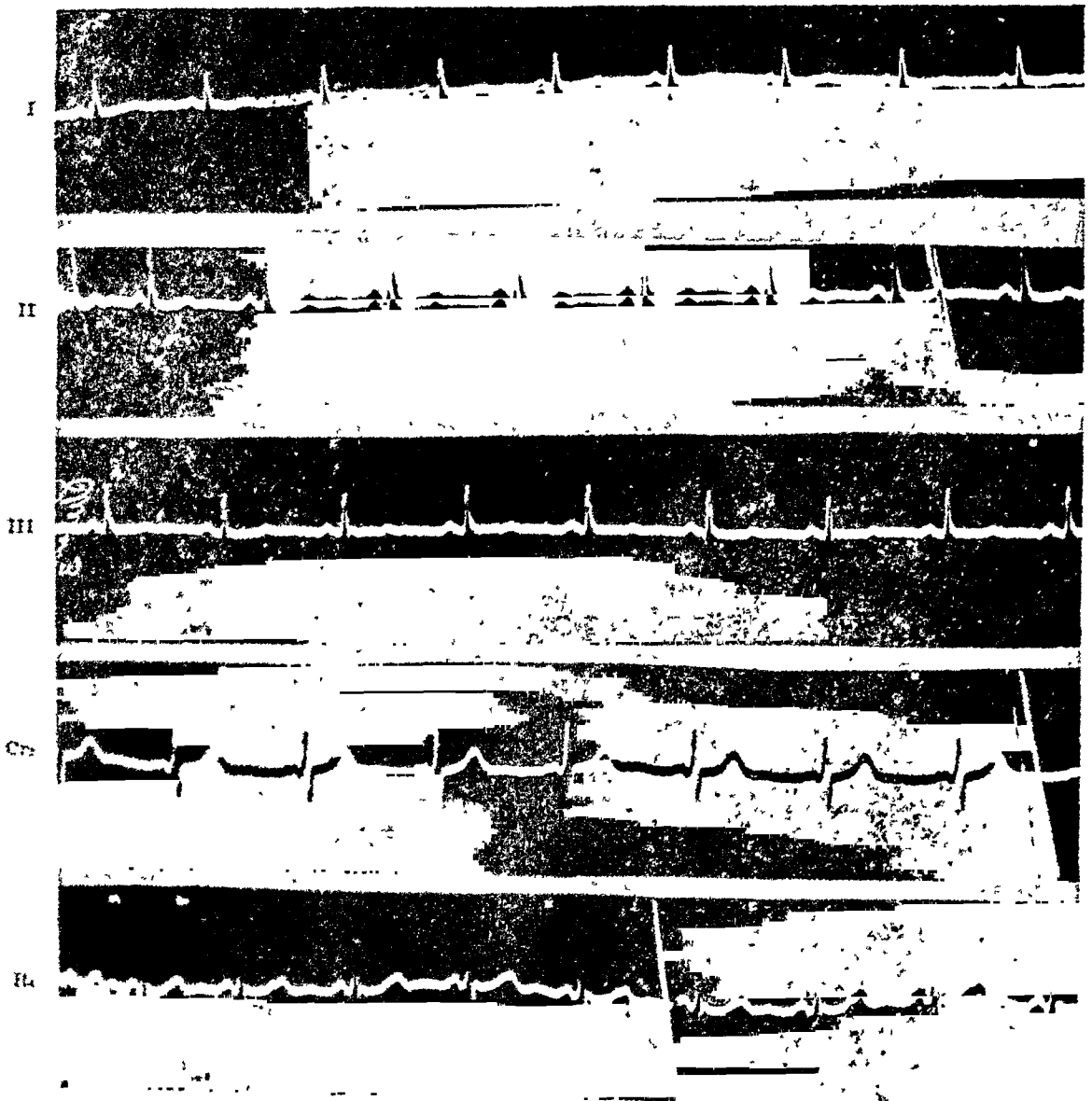


Fig. 2F.—On Jan. 26, 1943, the T waves were upright in all leads.

seen six days after an attack and had a normal electrocardiogram, but the next two attacks produced T changes. A recent communication (Feb. 8, 1944) with the patient was encouraging. He had had only three light attacks and had gained in weight and strength.

There are a few changes in these tracings differing from the usual patterns of coronary occlusion: The S-T changes are depression in all leads with T-wave inversion during the stage of tachycardia. Also there are no Q waves. No more than 5 c.c. of diglusion were required to stop the first attack. No more

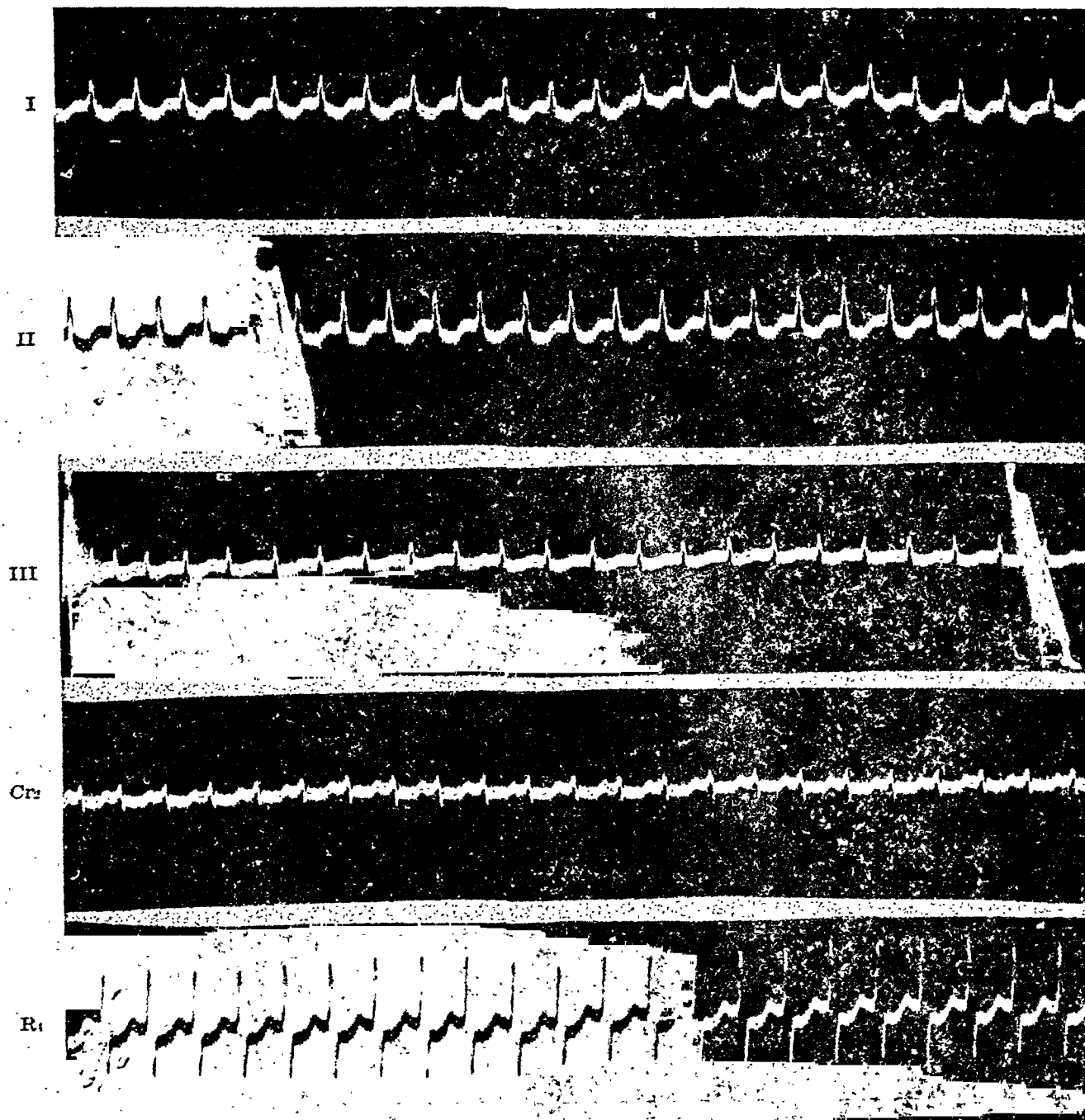


Fig. 3A.—Electrocardiogram taken on Feb. 11, 1943, three days after onset of attack. The rate was 200 per minute. Note notching of QRS complexes, depression of S-T segments in all leads, and T-wave changes.

digitalis was given. Consequently, it was not a digitalis effect that maintained the T changes after cessation of the tachycardia. Seeing this type of patient for the first time shortly after an attack and obtaining this type of tracing certainly puts one on the alert.

We agree with Geiger that the probable cause of these changes is a temporary ischemia to an area of myocardium which heals by resolution rather than scarification. This patient suffered ischemic pain as suggested by distress in the epigastrium and radiation into the neck.

SUMMARY

A case is presented of paroxysmal auricular tachycardia producing electrocardiograms simulating posterior myocardial infarction after cessation of the tachycardia. It was shown that there were no constant structural or medicinal factors affecting the electrocardiograms. The return to normal was too rapid for a real occlusion. However, it is felt that the basis for the patient's pain and T changes was due to a temporary ischemia. This is another condition that can cause T-wave changes; it must be borne in mind because of the difference in

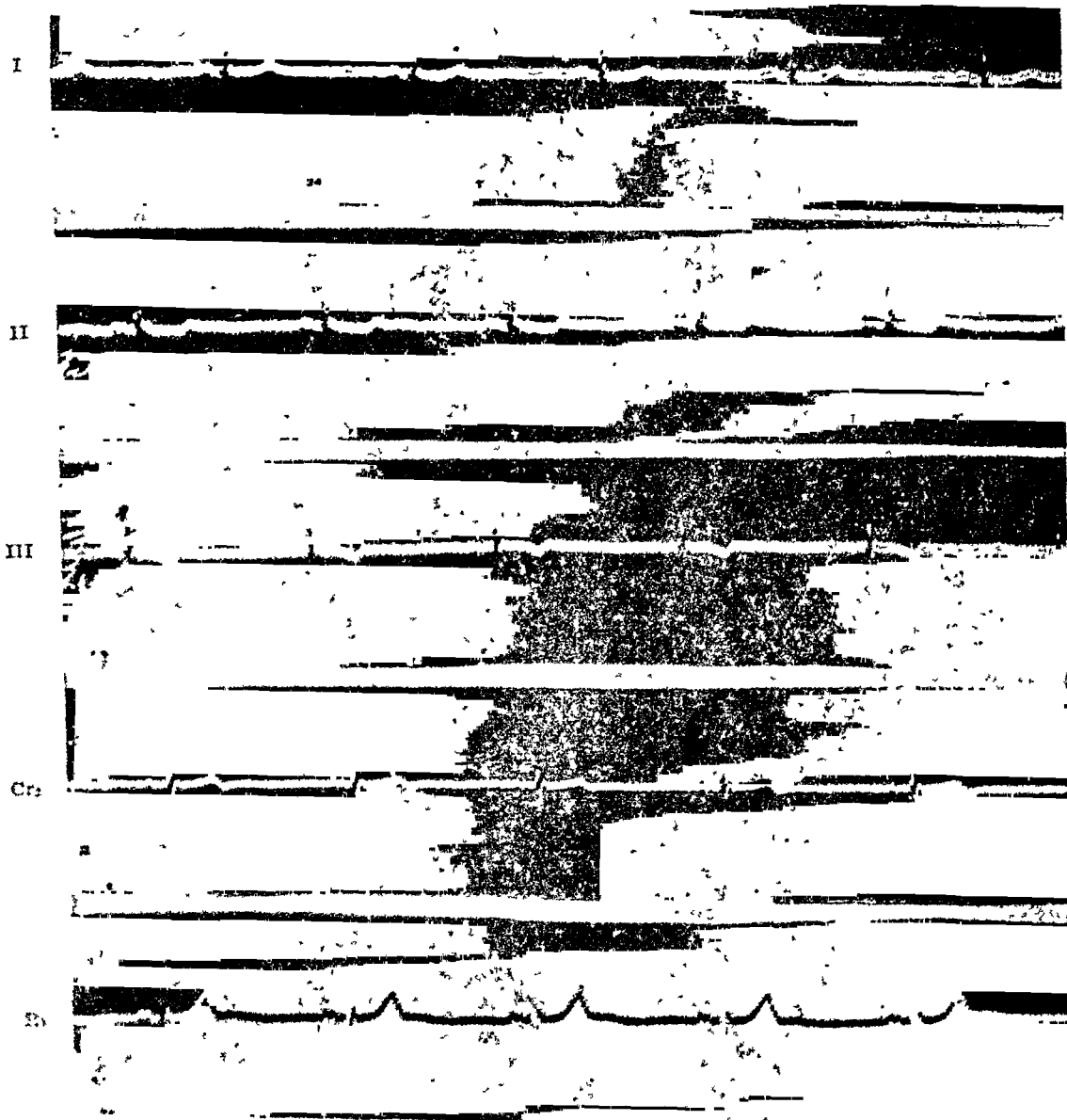


Fig. 2B.—This electrocardiogram, taken on Feb. 23, 1943, fifteen days after the second attack, shows T_2 and CR_2 to be diphasic and T_1 inverted. There is still notching in all QRS complexes.

prognosis. A careful and detailed history of the attack or attacks, progress studies, and the slight differences between this pattern and the usual coronary patterns will enable one to make a correct diagnosis and prognosis.

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HEART TUMOR: REPORT OF A CASE

MAJOR ROBERT A. STEVEN, M.C.

THIS case is reported because of several unusual features which made an accurate ante-mortem diagnosis difficult.

The patient was a 25-year-old soldier with no previous pertinent illness except for a questionable pneumonia in 1942. There was no history of rheumatic infection. His parents were living, and his father, aged 50 years, had heart disease. Two siblings were living and well.

The soldier first became ill on April 15, 1943, with anorexia, night sweats, cough, palpitation, shortness of breath, and loss of weight. Between then and May 1 he lost 12 pounds. He also had nonradiating retrosternal pain, described as an ache or a weight or pressure, associated with his shortness of breath. On May 1 he was admitted to an Evacuation Hospital and after five days developed a high fever, a rapid thready pulse, cyanosis, orthopnea, and peripheral edema. On May 5 he was transferred to Torney General Hospital where he was admitted to the Contagious Disease Section. The transfer diagnosis was lobar pneumonia involving the right lower lobe. He received 18 Gm. of sulfathiazole at the hospital. The white blood cell count on May 2 was 4,700 with 73 per cent polys, and on May 5 it was 4,550 with 80 per cent polys. Red counts on the same dates were 3.96 and 4.5 million.

On entry the nurse noted a pulse of 128, respirations of 28, and temperature of 102.2° F. Examination by the Chief of the Contagious Disease Section showed the following positive findings: scattered skin lesions on all extremities, some macular, others ulcerative, and some healed with thin scars (the dermatologist made a diagnosis of erythema multiforme); orthopnea and marked cyanosis of the face, neck, upper chest, and nail beds; injected throat and some post nasal drip; no adenopathy; normal thyroid; lagging of the right chest and dullness, diminished breath sounds, many fine râles at the right base, and a pleural rub in the axilla; pulse weak and thready with a rate of 144 per minute; gallop rhythm at the apex; no murmurs; heart sounds of fair quality; blood pressure 100/82; tender liver 5 fingerbreadths below the right costal margin; edge of the spleen palpable; 1 plus edema of legs but no sacral edema; neurological examination negative; no ascites.

Later in the day, I was asked to examine the soldier in view of his cardiac findings. There was orthopnea and some cyanosis of the fingers, toes, and face even when he was in the oxygen tent, although much less than when he was out of the tent. He was complaining of pain across the front of the chest and pain with deep breathing. The point of maximum intensity was just outside the mid-clavicular line in the left fifth intercostal space. There were no thrills or friction rub. There was a gallop rhythm at the apex. The sounds were faint at the apex, but much louder over the base. There was a rough, swishing, systolic murmur medial to the apex. The pulse rate was 144. The chest signs were as given previously. There was gross enlargement of both lobes of the liver and 1 plus edema of the feet and ankles. The preliminary impression was acute myocardial failure precipitated by pneumonia of undetermined etiology. The treatment instituted was rapid intravenous digitalization, salyrgan with theophyllin, whisky, and caffeine when necessary. He was also given sulfadiazine for several days because of the signs of pneumonia.

Blood: Red blood cell count, 3,610,000; hemoglobin, 85 per cent; white blood cell count, 5,250; neutrophils, 70 per cent; lymphocytes, 29 per cent; eosinophiles, 1 per cent; morphology, normal. Sulfathiazole blood level was 6 mg. per cent. Urine: specific gravity, 1.032; albumin, negative; sugar, negative; Microscopic examination, normal except that crystals resembling sulfathiazole were present. Blood Kahn reaction was negative. Sputum was negative. A portable x-ray of the chest showed areas in the right upper and right base suggestive of consolidation, and considerable enlargement of the heart was suggested. His cardiographic tracing is seen in Fig. 1. Several red blood cell counts during the course of his illness showed a mild reduction, while others were within normal limits, but all the

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hemoglobin determinations were normal. Several sputa were negative for acid-fast organisms. Altogether six cardiograms were obtained, and all were essentially alike. Many urinalyses were done, and all were essentially negative except for albuminuria which varied from none to 1 plus.

Progress Notes.—May 6: Temperature, 98° F.; pulse, 116; peripheral edema nearly gone; liver, 3 fingerbreadths below the costal margin. No cyanosis was present while the patient was in the oxygen tent, and breathing was easier. Output during the night was 900 c.c., and sweating had been profuse. Eleven cat units of digitalis were administered intravenously in eighteen hours; also, 2 c.c. of salyrgan were administered intravenously. P₂ was accentuated. Gallop rhythm was gone. Some râles were present at both bases. The patient seemed greatly improved and very cheerful. His electrocardiogram indicated that posterior infarction was at that time a possibility.

May 7: All edema gone; pulse, still 112; liver, still smaller. Systolic apical murmur was at that time very faint and soft and blowing, due possibly to improvement in the cardiac dilatation. Sulfadiazine level was 19.6 mg. per cent.

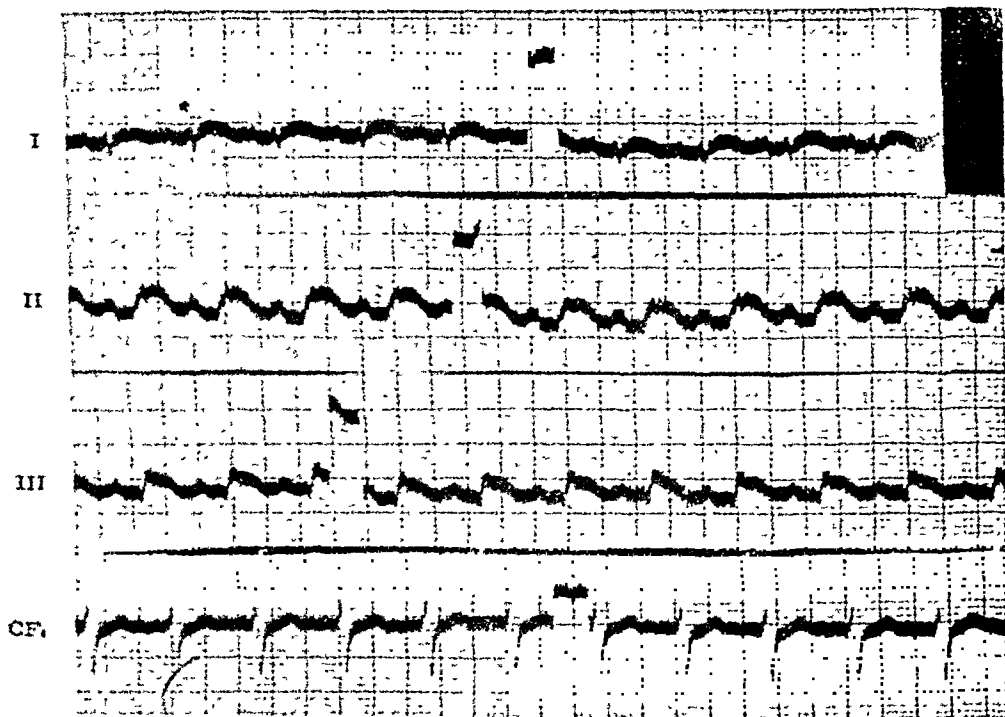


Fig. 1.—Electrocardiogram taken May 11, 1943.

May 8: Blood pressure, 92/58; pulse, 116; afebrile. Intake (twenty-four hours), 780 c.c.; output, 510 cubic centimeters. Cough gone. No edema.

May 9: Blood pressure, 80/60; pulse, 124 (paradoxical pulse); respirations, 16; temperature, 101° F. Later in the day the patient became very dyspneic; his blood pressure was 76/70. The heart sounds were faint. Tamponade of the heart was considered, and a pericardial tap was done. Ten cubic centimeters of clear yellow fluid were obtained which, in the light of further developments, was probably pleural transudate. Late in the day his temperature was 103.6° F., his pulse was 144; and his blood pressure was 102/70. The white blood cell count was 4,250 with 85 per cent polys.

May 10: Pulse, 144; respirations, 28; blood pressure, 112/88; sounds, distant; gallop rhythm present; no peripheral edema; liver down 2 fingerbreadths. The patient appeared critically ill. Morphine was started. The white blood cell count was 7,500 with 87 per cent polys. The sedimentation rate was 5.2 mm. per hour.

May 11: Dyspneic; cyanotic; pulse, 120; respirations, 28; blood pressure, 108/88; liver at level of navel. Blood culture (eighth day) was still sterile. Sulfadiazine was stopped. Maintenance doses of digitalis were continued. One plus edema was present; râles were heard at both bases. A paradoxical pulse was present. The area of cardiac dullness was widened. Some bloody sputum could be raised.

May 14: Six hundred cubic centimeters of serosanguineous fluid were removed from the left side of the chest. Nonprotein nitrogen was 72 mg. per cent. Salyrgan administration was stopped. Sulfadiazine level was 13 mg. per cent. Sedimentation rate was 20 mg. per cent. Smears and aerobic and anaerobic cultures of the pericardial (pleural) fluid were negative.

May 15: White blood cell count was 12,300 with 84 per cent polys. Three plus edema of the lower legs and sacrum was present.

May 17: Some coffee-ground emesis and abdominal distention were present. The blood pressure was 92/66, and the pulse was 120. The patient was getting steadily worse. White blood cell count was 8,700 with 86 per cent polys.

May 19: The patient continued to have coffee-ground emesis. During the preceding two days he had been given glucose intravenously. Nonprotein nitrogen was 103; creatinine was 2.2. He was given 250 c.c. of whole blood. The white blood cell count was 10,400 with 97 per cent polys.

May 20: Temperature, 99.4° F.; pulse, 116; blood pressure, 90/60; paradoxical pulse; gallop rhythm; a variable high-pitched diastolic murmur in the fourth intercostal space, and a to and fro soft systolic blow at the apex; Cheynes-Stokes respirations; râles at both bases; tender, questionably pulsating liver nearly to navel; slight peripheral edema and signs of ascites; pupils small and fail to react to light; tongue crusted and dry; and teeth and gums coated. He passed a tarry black stool. The white blood cell count was 10,850 with 94 per cent polys.

May 21: Shortly after intravenous administration of glucose the patient suddenly gave a gasp and died. A second blood culture, taken just before death, showed a growth of *Streptococcus viridans* four days later.

Autopsy Findings.—Positive findings only from the autopsy report follow. The pathologic diagnoses were concurred in by the Surgeon General's office.

Several maculopustular skin lesions, covered by thick crusts, varying from 1 to 3 cm. in diameter, were present on the chest and extremities. The liver was 3 fingerbreadths below the costal margin. About 100 c.c. of clear yellow fluid were present in the peritoneal cavity. On the serosa of the jejunum and ileum in the lymphoid tissue, opposite the attachment of the mesentery, were about eight whitish, sharply demarcated plaques, varying from 0.6 to 2 cm. in diameter, surrounded by indistinct hemorrhagic zones and induration. The vessels leading to these areas were prominent. The mucous membrane opposite each of these plaques was the site of an ulcer. All these ulcers were transverse, their edges were elevated and indurated, and in places, were covered with reddish black material. Sections through these ulcers showed massive infiltration by cells similar to those described in the heart below. Each pleural cavity contained 1 liter of clear yellow fluid. The heart was enlarged and prominently occupied the anterior mediastinum. The pericardial sac contained about 5 c.c. of clear yellow fluid. There were fibrinous adhesions between the pericardium and epicardium. The heart weighed 460 grams. The epicardium was rough and covered by a layer of shaggy fibrin. In several places, especially over the posterior surface of the left ventricle, the epicardium was whitish and greatly thickened. The right auricle was of normal size, and its endocardium was smooth. The foramen ovale appeared functionally closed but showed a slitlike opening which admitted a large probe. The right auricular appendage was empty. The coronary sinus appeared normal. The tricuspid valve and its chordae tendineae and papillary muscles were normal. The right ventricle was slightly dilated; its endocardium was smooth; and its muscle was quite pale with a yellowish-white tint in places. Cross sections show the myocardium to be replaced in several places by a soft homogeneous tissue which obscured the normal fibrillar structure of the myocardium. The pulmonary valves were normal. The pulmonary aorta contained a clot of blood. The left auricle was large; its endocardium was smooth; and its wall was thin. The left auricular appendage was empty. The mitral valve was normal in all respects. The left ventricle was greatly dilated. Its endocardium was smooth and showed many irregularly shaped, sometimes confluent, areas of yellowish-white discoloration. No thrombi were present. Cross section showed a yellowish-white tissue replacing much of the myocardial wall, and in such areas the fibrillar structure of the myocardium had entirely disappeared. These areas varied in size from small flecks to areas measuring 4 and 5 centimeters. This occurred in all parts of the heart including the inter-

ventricular septum. The aortic valve was normal in all respects. Except for occasional yellowish-white plaques on the intima of the larger branches, the coronary system was normal. The wall of the aorta was quite thin, and the lumen was comparatively small, especially the abdominal portion. There was an area of bluish-red discoloration on the posterior aspect of the left lower lobe and another on the medial margin of the left upper lobe, each measuring about 4 cm. in diameter. Cross section of the area in the lower lobe showed a wedge-shaped, blackish-red portion under the pleura. No thrombus or embolus was seen in the vessels below this area. The area in the upper lobe appeared as a typical hemorrhagic infarct. In the right lung several areas of bluish-red discoloration were seen under the pleura which on section seemed to be hemorrhagic infarcts. The spleen weighed 115 grams. The liver weighed 480 grams, and its consistency was firm. The gall bladder, pancreas, and adrenals were normal. The left kidney, ureter, renal artery, and seminal vesicle were absent. The right kidney weighed 180 grams and was grossly normal. The bladder contained no left ureteral orifice. The right seminal vesicle and the prostate were normal. The testes were normal.

MICROSCOPIC

Left Ventricle.—The serosal cells of the epicardium were mostly missing and replaced by thick strands of hyaline fibrin which was being organized. In a few places several layers of somewhat irregularly arranged serosal cells were present. The epicardium was greatly thickened due to the presence of edema, fibrin, granulation tissue, and infiltrations of lymphocytes, plasma cells, and monocytes. The subepicardial fat tissue was, in several places, densely infiltrated by tumor cells which were round or polyhedral in shape showing rather large, round or oval, chromatin-rich nuclei with indefinite nucleoli. The cells were fairly uniform but the nuclei varied somewhat in size, shape, and staining characteristics. Many mitotic figures were seen, some of which were quite irregular. The tumor cells had invaded the septa of the fat tissue and had replaced many of the fat globules. In one place tumor cells were seen to invade the epicardium and there was extensive invasion of the myocardium. Tumor cells were present, especially in the larger septa, but also about the individual myocardial fibers causing vacuolar degeneration, atrophy, and necrosis of many of the fibers. A papillary muscle seen in the section also showed massive invasion by tumor cells and a thick layer of tumor was present beneath the endocardium. The remaining portion of the myocardium showed moderately hypertrophied fibers with distinct striations. Most of the nuclei were vesicular, and there was a moderate amount of lipochrome pigment about the poles of the nuclei. A portion of the mitral valve showed edema but was otherwise normal. One lymphatic vessel seen in the subepicardial fat tissue contained tumor cells.

Right Ventricle.—Most of the myocardium was extensively infiltrated by tumor cells growing in a fashion similar to that described above. In a few areas the myocardium was entirely replaced by tumor. There was extensive necrosis of parts of the myocardium and of the tumor tissue. The lumina of several vessels of the myocardial septa were solidly filled with tumor cells; these vessels appeared to be lymphatic. The epicardium showed changes similar to those above. Again, as previously, muscle tissue of a papillary muscle showed massive invasion by tumor.

Interventricular Septum.—There was massive invasion of a portion of the septum by tumor, and in such places the heart muscle fibers show changes similar to those above. The septum was markedly thickened by edema. In places the endocardium was infiltrated by tumor. No Purkinje fibers were recognized.

With a Font-Bielschowsky stain the argentophil fibers were well preserved except for small areas of necrosis where some of the fibers were broken up. There was no increase in reticulum fibers in the areas infiltrated by tumor. With the oxidase stain no oxidase granules were demonstrated in the tumor cells. The outer layer of the adventitia of the aorta was thickened and covered with masses of bulky hyaline fibrin which was being organized. Beneath this there was granulation tissue.

Except for hemorrhagic infarcts, edema, emphysema, and fibrinous pleurisy secondary to the infarcts, the lungs were clear.

Essential pathologic diagnoses were:

1. Multiple lymphosarcoma of the jejunum and ileum with metastases to the skin and heart.
2. Cardiac hypertrophy, subacute fibrinous pericarditis, and pleurisy, hydrothorax, passive hyperemia of spleen and liver, secondary to 1.
3. Congenital aplasia of left kidney, ureter, and seminal vesicle.

COMMENT

When the patient was first seen the outstanding clinical features were fever, leucopenia, physical and x-ray signs of pneumonitis, and obvious congestive heart failure, all of which were interpreted as virus pneumonia with secondary cardiac failure. Possibly the sulfonamide was the cause of the low white blood cell count. When the first electrocardiogram was seen, a posterior infarction was suggested by the elevated S-T segments in Leads II and III. Serial tracings failed to show the usual progression of changes seen in infarction. Clinical features then suggested cardiac tamponade, which was not verified by two taps. Tumor was not suspected. The primary lesions in the bowel gave rise to no symptoms except possibly the coffee-ground vomitus and tarry stool terminally, so that, from a diagnostic standpoint, the tumor was as difficult to discover as a primary cardiac neoplasm is.

No review of the literature will be given as there have been several in recent years, including one by Lisa and his co-workers.¹ Incidentally, their Case 1, a female, aged 17 years, also suffering from a metastatic lymphosarcoma, ran a course very similar to that of our case, although the electrocardiograms in the two cases were very different.

Intractable cardiac failure with no clear-cut etiology, mentioned by numerous writers as common in cardiac neoplasms, is again illustrated by this case. It was impossible, however, to definitely rule out rheumatic heart disease with mitral insufficiency.

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ACUTE RHEUMATIC HEART DISEASE IN THE AGED, WITH REPORT OF A CASE WITH STOKES-ADAMS SYNDROME TREATED WITH PAREDRIE

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ACU TE rheumatic heart disease is fairly common among young persons, but it is rare in the aged. The initial attack of rheumatic heart disease occurs between 5 and 11 years of age, according to the data of Leonard.¹ On the other hand, active rheumatic heart disease is rare after 50 years of age. Rothschild, Kugel, and Gross² found only two cases in the sixth decade of life and one in the seventh decade, and Rakov and Taylor³ reported another case in the seventh decade. The purpose of this report is to record a case of an initial attack of rheumatic heart disease which developed at 64 years of age, was characterized by a Stokes-Adams syndrome of unusual severity, and was treated with paredrine, at times in large doses.

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CASE REPORT

A white man, aged 64 years, had always been well and had participated in vigorous physical activity. His principal hobby was mountain climbing, and he took long hikes daily. On Nov. 12, 1942, he noted headache, generalized aching, and painful muscles and joints, particularly of the lumbar region and wrists. Three days later he consulted one of us (A. W. B.), at which time his temperature was 102° F. The wrists were not red, hot, or swollen. During the next two weeks the fever and aching persisted, but the joint manifestations moved to the shoulders, hips, knees, and ankles. The manifestations subsided during the third week of the illness, and he was permitted to be out of bed for increasing periods daily. During the evening of December 2, he walked into another room, became unconscious, and fell. The attack occurred without warning, and subsided very soon after he had fallen. A few minutes later nothing abnormal could be ascertained by physical examination, except a contusion of the scalp from the fall. At approximately 3 o'clock the following morning, he was awakened by a "peculiar feeling," and, during the next few minutes, was observed to have three convulsions of only a few seconds' duration. Physical examination a few minutes later revealed nothing unusual. The pulse was regular and of normal rate and contour, and the blood pressure was 140/80. During the next three hours five more convulsions were observed; they were characterized by jerking of the arms and hands, slight opisthotonos, and labored respiration. They lasted approximately five seconds, and occurred without warning, without loss of sphincter control, and without demonstrable residual manifestations. The attacks became more frequent, occurring every few minutes, and asystole was found to be present during the attack. A diagnosis of Stokes-Adams syndrome was made, and he was admitted to Mercy Hospital, in Iowa City, Iowa. An electrocardiogram, Fig. 1, showed periods of complete auriculoventricular block, with ventricular asystoles.



Fig. 1.—Complete auriculoventricular block, with periods of ventricular asystoles, are seen in Lead II the morning of the first day in the hospital.

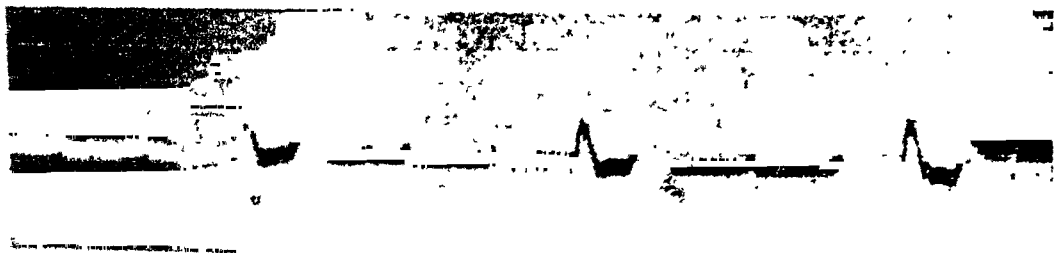


Fig. 2.—Complete auriculoventricular block and left bundle branch block are observed in Lead I on the afternoon of the first day in the hospital.

The intravenous administration of 7½ grains of theophyllin ethylenediamine, and the oral and subcutaneous administration of ¼ grain of ephedrine did not decrease the frequency of the attacks. Convulsions continued at three- to five-minute intervals, and lasted fifteen to thirty seconds, for four hours. At this time parendrine, in doses of 60 mg., was administered orally every two hours. After the third dose, four hours later, the convulsions became less frequent and of shorter duration, and one and one-half hours later they ceased. An electrocardiogram, Fig. 2, revealed complete auriculoventricular block, with delayed conduction in the left branch. An abnormally high T wave in Lead IV, Fig. 3, indicated myocardial disease. The complete heart block continued for two days, when it changed to a two-to-one auriculoventricular block (Fig. 4). During this time he received 1,320 mg. of parendrine, or approximately 50s mg. daily. At approximately noon of the third day the pulse rate suddenly increased to 120 beats per minute and became irregular. An electrocardiogram confirmed the diagnosis of auricular fibrillation. Parendrine was discontinued, but the fibrillation continued

until noon of the following day, at which time the pulse rate decreased to 90 beats per minute and became regular. An electrocardiogram showed normal mechanism. Paredrine therapy was resumed, and 240 mg. were administered during that afternoon and evening. Auricular fibrillation recurred and disappeared six hours after paredrine was discontinued. The following day paredrine was resumed in doses of 60 mg. three times daily.

During the second day in the hospital the temperature began to rise, and it reached 102° F. the next day. The respirations increased to 40 per minute, the right shoulder became painful and tender, and the patient became irrational. Within ten hours after the institution of salicylate therapy, the temperature and respirations had returned to normal, but during the next five days the temperature rose to 99.6° F. in the afternoon, and the ankles became very tender. During the next eight days he became rational and the joints gradually improved.

The cardiac manifestations had apparently become stabilized, with normal mechanism, but the systolic arterial pressure had risen to 170 mm. Hg. The dose of paredrine was reduced to 40 mg. three times daily, and two days later to 20 mg. four times daily. At approximately noon on this day, the thirteenth day in the hospital, convulsions recurred and continued at two- to three-hour intervals for the next three days. An electrocardiogram showed frequent periods of ventricular asystole, interrupted by numerous ventricular extrasystoles. Convulsions, very probably, would have been more frequent if it had not been for these ventricular extrasystoles. The temperature rose to 102° F., and paredrine was resumed in doses of 100 mg. five times daily. Convulsions ceased two days later, and the following day the temperature returned to normal. Nothing of significance occurred for twenty-two days, during which time paredrine was continued in the doses mentioned. An electrocardiogram obtained during this time showed delayed conduction in the right branch of the bundle.

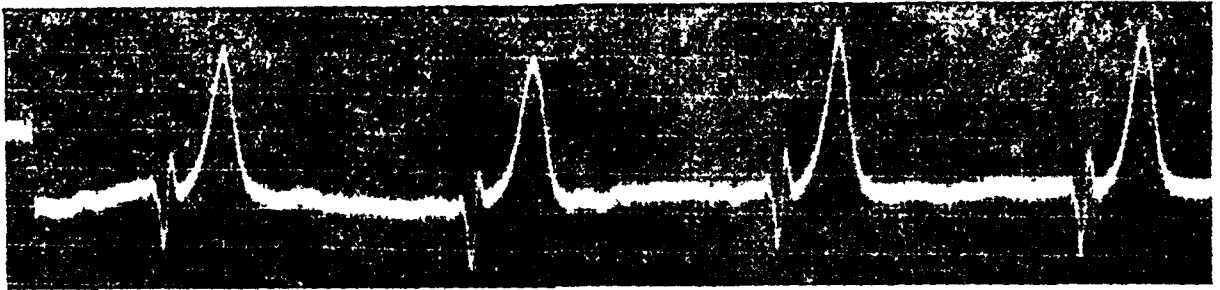


Fig. 3.—The abnormally high T wave in Lead IVF on the morning of the second day in the hospital.

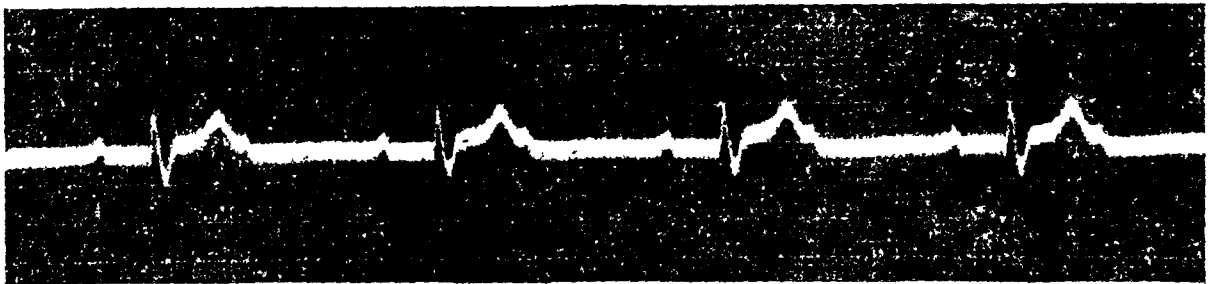


Fig. 4.—The two-to-one auriculoventricular block in Lead I on the morning of the third day in the hospital.

Convulsions and fever returned at approximately 7 A.M. on the thirty-eighth day in the hospital, or twenty-three days after the last recurrence. The convulsions occurred at approximately hourly intervals and lasted ten to twenty seconds. During the first day of this recurrence the paredrine was increased from the usual 500 mg. to 1,400 mg., and, in addition, 2 c.c. of epinephrine in oil were administered intramuscularly. An electrocardiogram revealed periods of ventricular asystole, interrupted by frequent ventricular extrasystoles. The next morning the cardiac condition was unchanged, and the convulsions continued. In spite of this, all medication was discontinued in the hope that complete auriculoventricular block would develop and the periods of asystole and convulsions would cease. The convulsions decreased and ceased at approximately 4 P.M. that day, but the pulse continued irregular, with short periods of ventricular asystoles for the next five days. The temperature remained elevated to 100° F. for the next four days, and then gradually returned to normal.

During the second day of this recurrence the ankles, knees, and wrists became red, hot, swollen, and extremely tender. The manifestations gradually subsided except that the electro-

cardiogram continued to show delayed conduction in the right branch of the bundle. He was discharged from the hospital on the sixty-seventh day, and remained in bed at home for three and one-half months, at which time an electrocardiogram, Fig. 5, showed the Wilson S-type of right bundle branch block and a grossly abnormal Lead IVF. He gradually increased his activity for one year without evidence of recurrence.

The leucocyte count was 17,000 upon admission to the hospital, declined to 10,700 at the time of discharge, and has remained from 7,000 to 8,000 since. The erythrocyte count, hemoglobin, and urine were normal throughout his illness, and the blood Wassermann reaction was negative.

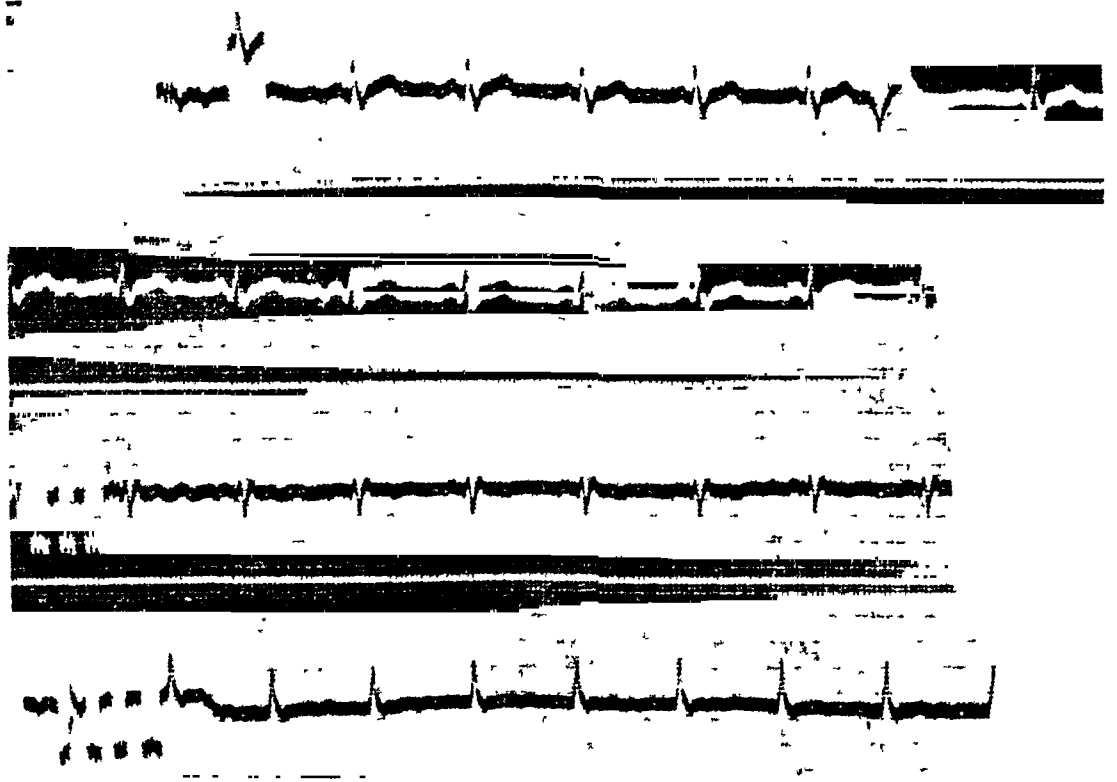


Fig. 5.—The Wilson S-type of right bundle branch block and grossly abnormal curve in Lead IVF are seen in the electrocardiogram taken three and one-half months after the last recurrence.

COMMENT

Lesions in the auriculoventricular node have not been prominent in the reported cases of rheumatic heart disease in the aged. Delayed conduction, on the other hand, is fairly common in younger persons. The Stokes-Adams syndrome is extremely rare in rheumatic heart disease at any age. It is difficult to ascertain in our case whether or not the auricular fibrillation and ventricular extrasystoles were due to the rheumatic heart disease or to the paredrine.

Nathanson, Engelberg, and Hersh⁴ reported encouraging results with the use of paredrine in the treatment of heart block. Of their six cases, partial block was eliminated in one of two cases, the ventricular rate was increased in the other, and the block was changed from complete to partial in two of four cases. They administered 60 mg. of paredrine three times daily, and emphasized that the pressor effect was less than with other preparations of this series of drugs. The oral administration of 80 mg. of paredrine increased the systolic pressure an average of 69 mm. Hg, and the duration of the effect was two hours. They pointed out that the stimulating effect upon the conduction of the heart was relatively greater with this preparation, but they employed small doses as compared to those employed in our case. They stated that the drug is destroyed

in the gastroenteric tract in some cases, and that the drug is unsuitable in such instances.

It is difficult to evaluate the effect of paredrine in our case. The apparent improvement following the initial administration of the drug was due to the development of complete heart block, and not to the elimination of the block. Was the auricular fibrillation which developed after three days of over 500 mg. of paredrine daily due to the paredrine or to the rheumatic heart disease? The fact that the arrhythmia disappeared the day after discontinuing paredrine and recurred after the medication was resumed, and then disappeared again after the therapy was stopped for the second time, suggests that the drug was the exciting cause. On the other hand, doses of over 500 mg. of paredrine were resumed eight days later and continued for twenty-six days without producing auricular fibrillation. It appears, therefore, that the rheumatic fever was the principal factor in the production of the auricular fibrillation. We must consider, however, that it is possible that the drug was effective at first and later it became destroyed in the gastroenteric tract and was ineffective.

It appears doubtful that the drug was a factor in the production of the ventricular extrasystoles. During the second recurrence, the thirteenth day in the hospital, the dose had been reduced to only 80 mg. daily, and ventricular extrasystoles were prominent. In addition, ventricular extrasystoles continued during the last recurrence for five days after the drug had been discontinued. The fact that these disturbances in conduction occurred each time during reactivation of the rheumatic fever is additional evidence that the disease and not the drug was the principal factor in their production.

The largest dose of paredrine we have been able to find in the literature is 400 mg. daily, which was administered by Korns and Randall.⁵ In their case this dose controlled the hypotension without the nervous stimulation which was experienced with benzedrine. They did not observe any unusual effect upon the conduction in the heart. Because of the pressor effect of paredrine, we were hesitant to use such large doses, but the increase in arterial pressure observed at the initial administration of the drug, i.e., from 140 to 170 mm. Hg, was the greatest increase which we observed.

SUMMARY

A case is reported in which the initial attack of rheumatic heart disease occurred at 64 years of age, and was characterized by complete heart block and a Stokes-Adams syndrome of unusual severity and duration; the latter was treated with unusually large doses of paredrine.

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Abstracts and Reviews

Selected Abstracts

Shore, R., Holt, J. P., and Knoefel, P. K.: Determination of Cardiac Output in the Dog by the Fick Procedure. *Am. J. Physiol.* 143: 709, 1945.

The oxygen content of blood frequently differs when drawn simultaneously from the two venae cavae, from two points in the right auricle, or from the right auricle and right ventricle in dogs in barbital anesthesia. Estimation of cardiac output in the barbitalized dog by the Fick procedure with blood taken from the right auricle may be in considerable error as a result of obtaining a nonrepresentative sample of mixed venous blood.

There is a progressive decrease in cardiac output during the first four hours of barbital anesthesia in dogs.

AUTHORS.

Fenning, C., and Mott, C. R.: The Effect of Modulated High Frequency Condenser Field on the Straub-Fuehner Frog Heart Preparation. *Am. J. Physiol.* 144: 1, 1945.

Characteristic cardiac and ventricular standstill of the Straub-Fuehner frog heart can be produced using modulated, high-frequency current applied in the manner shown by the authors.

The results so obtained show a selective action of the current, the specific nature of which is not understood. It is believed that the selective action takes place on the nerve terminals, the pacemaker, and the associated conductive system. Selective heating may account for the results, since it is known that a high frequency electrostatic field will preferentially heat oils faster than salines. In addition, there is some evidence of chemical factors produced or activated during exposure.

AUTHORS.

Duomarco, J., Rimini, R., and Recrate, P.: Intraabdominal Pressure and the Pressure in the Inferior Vena Cava. *Rev. argent. de cardiol.* 11: 273, 1945.

In dogs, optical records were obtained simultaneously of the pressure in the abdominal cavity and the pressure of the inferior vena cava, at various levels, and of the right auricle.

The forms and absolute values of both curves are identical when the venous pressure is taken just below the diaphragm; at more distant levels there is a small difference due to the vis a tergo.

Over the diaphragm the venous pressure declines suddenly, and cardiac waves appear in the record which is then practically identical with the record of intrathoracic pressure obtained after a partial pneumothorax.

The pressure variations of the abdominal and thoracic cavities are reciprocally blocked at the level at which the inferior vena cava crosses the diaphragm; this block disappears when the vein is abnormally distended.

AUTHORS.

Brannon, E. S., Merrill, A. J., Warren, J. V., and Stead, E. A., Jr.: The Cardiac Output in Patients With Chronic Anemia as Measured by the Technique of Right Atrial Catheterization. *J. Clin. Investigation* 24: 332, 1945.

Twenty-four sets of data were obtained on eighteen anemic subjects. Atrial pressure readings and samples of mixed venous blood for determination of the cardiac output were obtained through a catheter introduced into the right atrium. The femoral arterial pressure was recorded optically by the method of Hamilton.

No consistent change in the circulation was observed when the hemoglobin level was above 7 Gm. per 100 milliliters. Below that level, the cardiac output at rest was increased, the arteriovenous oxygen difference and the peripheral resistance were decreased. The atrial pressure was not changed.

In four patients, observations were made before and after the hemoglobin had been doubled by transfusion or by the administration of liver extract. In each patient, the pulse rate fell, the diastolic and mean arterial pressures and peripheral resistance rose, and the cardiac output decreased.

When the hemoglobin level falls below 7 Gm. per 100 ml., the requirements of the body for blood are increased. This explains why anemic subjects may have circulatory insufficiency manifested by either shock or heart failure, while the heart is pumping as much as, or more than, would be required by a normal subject under similar conditions.

AUTHORS.

Warren, J. V., Brannon, E. S., Stead, E. A., Jr., and Merrill, A. J.: The Effect of Venesection and the Pooling of Blood in the Extremities on the Atrial Pressure and Cardiac Output in Normal Subjects With Observations on Acute Circulatory Collapse in Three Instances. *J. Clin. Investigation* 24: 337, 1945.

The effect on the circulation of the removal of 300 to 900 ml. of blood by venesection and the effect of pooling of blood in the extremities by the venous tourniquets were studied in twelve normal men. The atrial pressure readings and the samples of mixed venous blood for measuring the cardiac output were obtained through a catheter introduced into the right atrium by way of the antecubital vein. The femoral arterial pressure was recorded optically.

Venesection and the application of venous tourniquets caused a fall in atrial pressure from 20 to 65 mm. of water. There was no consistent change in cardiac output, mean arterial pressure, or peripheral resistance. Returning the blood by transfusion or by releasing the venous tourniquets was followed by a return of the atrial pressure to the control level without any change in the cardiac output.

The data suggest that the normal atrial pressure with the subject in the recumbent position is somewhat in excess of that required to fill the ventricles and that a decrease in blood volume of the degree reported here produces a lowering of atrial pressure without interfering with ventricular filling. These observations obviously do not apply to massive hemorrhage.

Acute circulatory collapse appeared in three instances. The subjects became pale, sweated profusely, and complained of nausea and weakness. The pulse rate slowed strikingly. The atrial pressure increased, the cardiac output remained unchanged. There was a marked fall in the arterial pressure and peripheral resistance. The circulatory collapse appeared to be the result of a sudden decrease in peripheral resistance because of reflex vasodilatation, presumably in the arterioles. There was no evidence of a decreased venous return.

AUTHORS.

Vizcaino, M., Pallarés, D. S., and Cabrera, E.: Certain Considerations Concerning Electrocardiogram Type S₁ S₂ S₃. *Arch. Inst. Cardiol. Mex.* 14: 261, 1945.

The authors studied the electrocardiograms of twenty clinically normal persons, fourteen persons with normal hearts and some other extracardiac process, and sixteen cardiac patients.

They confirm the findings of Ashman and Hull in regard to the normality of Types S₁ S₂ and S₃ and conclude that the majority of the tracings with low voltage are normal, even X, though they fail to fulfill the requirements postulated by the aforementioned authors, providing there is no other anomaly (other than low voltage). The examination should include careful study of the unipolar leads VR, VL, and VF and the precordial leads.

AUTHORS.

Hoff, H. E., and Nahum, L. H.: The Electrocardiographic Localization of Myocardial Infarcts by Injury Currents and Ventricular Extrasystoles. *Am. J. Physiol.* 143: 723, 1945.

Myocardial damage was produced in four regions of the dog heart by means of appropriate ligation of coronary arteries. These were (a) right and left ventricles exclusively, and (b) anterior and posterior regions involving adjacent portions of the right and left ventricles.

The changes in the S-T segment of the electrocardiogram in Leads I and III were the same as produced by potassium chloride injury in the same regions, namely, (a) depressed S-T segment with right ventricular damage, (b) elevated S-T segment with left ventricular damage, (c) elevation of S-T and depression of S-T₂ with anterior damage, and (d) depression of S-T₁ and elevation of S-T₂ with posterior damage.

The ventricular extrasystoles which appeared spontaneously after coronary occlusion showed configurations which indicated that they originated within the damaged area. They showed S-T segment changes which were the same as in the supraventricular complexes. Their configuration in the electrocardiogram may therefore serve as a localizing sign in myocardial damage.

AUTHORS.

Sabathié, L. G., Gaspary, F. V., and Rojas, R. A.: Unstable Intraventricular Block. *Rev. argent. de cardiol.* 11: 297, 1945.

Fourteen cases of nonpermanent intraventricular block were studied clinically and electrocardiographically. The denomination of "unstable" intraventricular block was adopted for these cases, classifying them as transitory or intermittent according to the circumstances.

In the mechanism of production of these blocks the modification of the refractory periods in both branches of the His bundle are of fundamental importance; the role of the precipitating factors, such as increased heart rate and vagal action, is also pointed out.

AUTHORS.

Leys, D. G.: Heart Block Following Diphtheria. *Brit. Heart J.* 7: 57, 1945.

The evidence that this case of complete heart block was due to diphtheria is: (1) the patient had severe diphtheria with neuritis at the age of 10 years; (2) subsequently a slow pulse was reported at the age of 22 years; and (3) she has complete absence of all tendon jerks without other evidence of nervous system disease.

AUTHOR.

Gómez, B. H., and Yépez, C. G.: Permanent Auricular Fibrillation in Two Brothers Without Evidence of Organic Heart Disease. *Arch. Inst. Cardiol. Mex.* 14: 251, 1945.

The authors present two cases of auricular fibrillation in brothers without apparent cardiac injury and without other evident cause. In other similar observations published, there also are no explanations to justify the alteration of the cardiac rhythm.

AUTHORS.

Pruitt, R. D., Barnes, A. R., Essex, H. E.: Electrocardiographic Changes Associated With Lesions in the Deeper Layers of the Myocardium. *Am. J. M. Sc.* 210: 100, 1945.

Myocardial injuries were produced in dogs by mechanical means. Damage to the endocardium and deeper layers of the myocardium of the apical portion of the left ventricle was attended by certain changes in the configuration of the QRS complex in a precordial lead designated apical IVR. Most constant among these changes was a reduction in the height of the R wave. The development of a Q wave or a notch low on the upstroke of the R wave were alternative types of change.

These changes in the QRS complex might be derived from: (1) injury to, or destruction of, the myocardial fibers adjacent to the endocardium; or (2) damage to Purkinje's network or the larger subdivisions of the left branch of the bundle of His.

Although in each of the twenty-two experiments under analysis there was accomplished an extensive destruction of those tissues in which portions of Purkinje's system are supposed to lie, in twenty experiments the width of the QRS complex remained unchanged. The speed at which the excitatory impulse was propagated apparently remained essentially unchanged, even though its course, as indicated by the form of the QRS complex, was altered. Also, a lesion high on the septum apparently not only is attended by a widening of the QRS complex, but also it is the only lesion likely to produce this effect.

Our results indicate that surface lesions exert a dominant influence on the level of the RS-T segment. We have suggested that this circumstance may prevail not because the traumatized subendocardial fibers fail to produce currents of injury, but because the resulting injury potentials are masked by the normal action currents arising in the uninjured superficial fibers in response to the excitatory process.

Changes in the T wave following injuries to the deeper layers of the myocardium were inconstant. The most frequently recurring alternation was an inversion of the T wave in a lead designated apical IVR.

AUTHORS.

Cameron, D. R.: Transient Heart Block and Coronary Occlusion in Pleural Shock. *Brit. Heart J.* 7: 104, 1945.

In the case here described, heart block existing during the acute phase may have been due partly to a vagal reflex; yet a more important factor, from the subsequent cardiogram, would appear to have been a coronary occlusion. The possibility of acute coronary insufficiency without occlusion, as described by Master (1944), is not a likely one; his cardiograms do not resemble those here described. It is hardly likely that a coincident coronary thrombosis took place. The close association with the attempted pneumothorax induction, together with the age of the patient, make this extremely unlikely. A wound of the heart can be excluded; the needle was never deep enough to have produced this. A clot disturbed from a thrombotic process in the pulmonary circulation might produce an embolism (Saphir, 1933), and this remains a possibility. It seems more reasonable to assume that an air embolism occurred.

As the typical changes indicative of coronary occlusion may take some little time to develop—up to a few hours (White, 1931)—this right axis deviation may have existed before the accident, as in Durant's case.

An interesting point is the absence of pain. Pain is evidently not one of the main features of this form of pleural shock. It may be that this absence of pain is a clinical characteristic of coronary air embolism, in contradistinction to other types of occlusion.

Heart block may occur more commonly in pleural shock than is thought, and Cocke remarks on bradycardia in two of his cases.

It is suggested that, in the case here reported, coronary air embolism occurred producing transient heart block and myocardial infarction.

AUTHOR.

Groedel, F. M., and Miller, M.: The Nature and Origin of the So-Called Systolic Gallop Rhythm. *Exper. Med. & Surg.* 3: 107, 1945.

Five cases with an apical mesosystolic click in the phonocardiogram and a slight displacement of the heart shadow in the x-ray film were demonstrated. In the cardiogram, the click was more like a murmur than a sound and appeared, distinctly, somewhat earlier over the vessels of the neck than at the apex of the heart. It was, therefore, obvious that the click originated in the close proximity of the heart, probably mostly in the larger pulmonary arteries. The cause of the click, in such cases, is most probably some constriction in this area, on the basis of minor pulmonary processes, which may occur during youth (calcified glands or minor pleuritic or pulmonary processes).

AUTHORS.

Bloomfield, A. L., Armstrong, C. D., and Kirby, W. M. M.: The Treatment of Subacute Bacterial Endocarditis With Penicillin. *J. Clin. Investigation* 24: 251, 1945.

Intensive penicillin therapy over long periods (approximately six to eight weeks) led to the following results in eleven patients with bacterial endocarditis caused by strains of streptococcus sensitive in the test tube.

All patients were promptly made "bacteria-free" (blood cultures) except one who died early in the course of treatment. Eight, or 73 per cent, were clinically cured of the infection after follow-up periods up to six months. One patient, apparently cured of the infection, died of cardiac failure. Cocci were seen in the depths of a scarred mitral valve. The significance of this observation is not clear. There were no clinical relapses or reinfections. Petechiae and emboli continued for some time after the blood cultures were negative. Renal lesions as evidenced by studies of urinary sediment were not as a rule completely eliminated by the treatment.

AUTHORS.

Dolphin, A., and Cruickshank, R.: Penicillin Therapy in Acute Bacterial Endocarditis. *Brit. M. J.* 1: 897, 1945.

Six cases of acute bacterial endocarditis—three due to hemolytic streptococcus, two to *Staphylococcus aureus*, and one to hemolytic streptococcus were treated with moderate doses of penicillin. Four of the patients were alive six to twelve months after penicillin therapy was stopped; three were well, and one had improved,

Attention is directed to the frequency of infection of healthy heart valves by streptococcus, which not uncommonly causes mild genital-tract sepsis, particularly after abortion.

The criteria for the diagnosis of acute bacterial endocarditis which may occur during the course of a generalized infection are discussed.

AUTHORS.

Arrillaga, F. C.: Segmentary Pericarditis. Arch. Inst. Cardiol. Mex. 14: 225, 1945.

A description is given of the radiographic features of the pericarditis that develop when the pericardium has adhesions or partitions produced by previous pericardial episodes (segmentary pericarditis). Four varieties may be distinguished, which yield characteristic radiologic pictures: the *left*, *right*, *superior*, and *inferior* segmentary pericarditis. The x-ray pictures supply the evidence of this classification.

AUTHOR.

Keith, J. D., and Ross, A.: Observations on Salicylate Therapy in Rheumatic Fever. Canad. M. A. J. 52: 554, 1945.

The oral administration of 13.3 Gm. (200 grains) of sodium salicylate with an equal quantity of sodium bicarbonate produces an average blood level of 31 mg. per cent. Ten grams (150 grains) of sodium salicylate with sodium bicarbonate produces a blood level averaging 27 mg. per cent.

Such levels are sufficient to control joint symptoms, keep the temperature down, and reduce the pulse rate. The sedimentation rate returned to normal in an average of four weeks in the group on 10 to 13.3 Gm. of salicylate and four and one-half weeks in the group on 0 to 1.7 Gm.

The incident of heart disease was approximately the same in the high salicylate group as in the low salicylate group. The numbers were not adequate to draw unequivocal conclusions. Ten per cent of the rheumatic patients who entered the hospital with normal hearts developed rheumatic heart disease that could be recognized at the time of discharge.

Nausea, vomiting, and tinnitus are much more common early in the administration of salicylates than after the patient has been receiving the drug for several days. These symptoms are not usually sufficient cause for stopping treatment. There was no evidence of kidney damage in this series. Three patients had toxic reactions characterized by hyperpnea. One of these might be labeled severe.

AUTHORS.

Fullerton, C. W.: The Prevention of Acute Rheumatic Fever. Canad. M. A. J. 52: 559, 1945.

Administration of 0.5 Gm. of sulfadiazine twice daily prevented the recurrence of acute articular rheumatism. This experience has been observed in 250,000 sailors during the winter months. The salicylates prevented the residual effects if they were continued long after an attack of rheumatism. The subjects treated prophylactically with sulfadiazine have been equally protected against scarlet fever and meningococcus meningitis.

AUTHOR.

Taran, L. M., and Jacobs, M. H.: Salicylate Therapy in Rheumatic Fever in Children. J. Pediat. 27: 59, 1945.

Rheumatic polyarthrititis responds promptly and effectively to large doses of salicylates. This result can be attained by both oral and intravenous use of salicylates. The intravenous route in our series of cases did not seem to offer significant advantages over the oral route provided the same plasma salicylate level is reached. No difficulty was encountered in reaching the desired plasma level with oral salicylate administration. The technical difficulties and the annoying symptoms ever present in the intravenous method of therapy in our experience outweigh the possible benefits derived from this method of shortening slightly the period during which rheumatic activity exists. Massive doses of salicylates in this group of cases did not present any thrombopenic disturbances and failed to show any detectable evidence of acidosis.

Massive doses of salicylates used in rheumatic carditis in children seem to produce equally prompt and effective results. The sedimentation rate returns to normal as promptly as in the polyarthritic group provided the therapy is instituted at the onset of rheumatic

activity. When therapy is postponed, the subsidence of the rheumatic process is delayed for many weeks. All other signs of carditis, however, subsided at the same time as the sedimentation rate returned to normal. Intravenous therapy in this group may be hazardous.

Small doses of salicylates do not seem to affect the course of rheumatic carditis. The carditis seems to follow the same course whether insufficient doses of salicylates are given or salicylate therapy is completely withheld. The duration of the active process as measured by the presence of an elevated sedimentation rate is much longer than in the group receiving massive doses of salicylates. Furthermore, when salicylates are withheld or given in small doses, the rheumatic process shows evidence of activity for a long period following the return of the sedimentation rate to the normal level.

AUTHORS.

Book Reviews

ENFERMEDADES DEL CORAZON—CIRUGIA Y EMBARAZO: By Ignacio Chavez, Director del Instituto Nacional de Cardiologia, México, D. F. Edición de el Colegio Nacional, Mexico City, 1945, 182 pages.

The author of this monograph is the director of the National Institute of Cardiology of Mexico City. He presents the results of personal experience in addition to extensive bibliographic quotations.

The book is well written and gives interesting and important data on two "borderline syndromes" of Cardiology, as it deals with pregnancy and surgery as a source of risk for the cardiac patient. It includes a detailed analysis of the hemodynamics of normal pregnancy and indications for the management of complications during labor and during surgical interventions.

The electrocardiographic changes and the auscultatory signs of normal pregnancy, the action of different hypnotics, and the pathogenesis and treatment of pulmonary embolism are some of the many interesting points of this book.

A. LUISADA.

VOLUNTARY HEALTH AGENCIES: By Selskar M. Gunn and Philip S. Platt. Ronald Press Co., New York, 1945, 364 pages. \$3.00.

Announcement

Due to conditions beyond the control of the editors and publishers, several issues of the JOURNAL are printed on an inferior grade of paper. Just as soon as the standard good grade of paper is available, its use will be resumed.

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The Association earnestly solicits your support and suggestions for its work. Membership application blanks will be sent on request. Donations will be gratefully received and promptly acknowledged.

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Original Communications

THE SYNDROME OF BERNHEIM

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THE clinical picture of right heart failure is routinely ascribed to dilatation of the right cardiac chambers. Thus, when systemic venous engorgement occurs in the hypertensive or arteriosclerotic subject, it is presumed that the right ventricle, having been unable to withstand the burden imposed by left ventricular insufficiency, has dilated and failed. That this is not always the case was demonstrated in 1908 by Bernheim who found stenosis rather than dilatation of the right ventricle in a large number of patients who had died with the classic symptomatology of right heart failure. In these cases he observed that encroachment upon the cavity of the right ventricle had resulted from deviation of a thickened interventricular septum which, in some instances, almost approximated the lateral wall of this chamber. It was evident from his findings that hypertrophy and dilatation of the left ventricle had materially reduced the capacity of the right ventricle through the mechanism of a bulging, interventricular septum. In some cases, the author found the latter chamber so compromised in its apical half that it appeared as a narrow slit between the bulging septum and the lateral wall with the result that only the upper half of the right ventricular cavity and the pulmonary conus remained open.

In 1910 and again in 1915, Bernheim^{1, 2} emphasized that the venous engorgement so characteristically observed in these subjects, is a direct consequence of obstruction to blood flow through the right ventricle and not, as is usually supposed, a manifestation of right heart failure. He pointed out that stenosis produced by septal bulging could be diagnosed during life if careful attention is paid to the evolution of symptoms. Thus, while the majority of cardiac patients with left ventricular hypertrophy manifest visceral congestion and edema only after dyspnea and pulmonary congestion have been present for some time, the former symptoms are the first to appear when stenosis of the right ventricle has supervened. Consequently, the diagnosis of Bernheim's syndrome rests upon the clinical picture of isolated right heart failure in association with left ventricular hypertrophy. These interesting observations, however, were forgotten until Laubry and his associates,³ having studied patients with similar signs, proposed, in 1924, a completely different interpretation.

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They contended that, since the picture of right heart failure is present in cases where the right ventricle is not dilated but narrowed, all instances of cardiac decompensation must actually be instances of left heart failure. Other students of the subject, however, challenged this point of view and supported Bernheim's original observations and conclusions. The publications of Martini and Joselevich,^{4, 8, 10, 17-19} Bullrich,^{5, 6} Mayer and Mazzei,^{7, 9} Mazzei,^{11-15, 21, 22} and others characterized the syndrome as possessing sufficient clinical and anatomic individuality to warrant its acceptance as an entity in clinical medicine.

In 1930, Mazzei,¹¹ on the basis of his own observations and those reported by others, divided the clinical picture of Bernheim's syndrome into two periods. The first, or anatomic period, is of variable duration and does not present important clinical signs. Interference with the filling of the right ventricle is counterbalanced by dilatation of the infundibular portion of the chamber and by enlargement of the right auricle. The second, or clinical period, has a shorter evolution and is itself divided into two stages. In the first stage, the signs of venous obstruction due to right ventricular stenosis become manifest. The pulmonary blood flow remains undisturbed, so that there is a dissociated failure of the circulation. In the second stage, which is usually terminal, stasis of the lesser circulation is added to the symptoms of systemic venous engorgement. Mazzei²¹ believed that the terminal appearance of pulmonary congestion in these cases signified failure of the right ventricle. Martini and Joselevich,¹⁷ however, took issue with this view. They maintained that failure of the lesser circulation is not observed in the first period of the syndrome because the dilatation of the left ventricle, which provokes deviation of the septum, is active and not passive. In the latter part of the second period, the appearance of râles at the lung bases presents evidence of passive dilatation and true failure of the left ventricle. Inasmuch as this end stage represents total failure of the heart, it is only the earlier period, according to Martini and Joselevich, which can be recognized as Bernheim's syndrome.

Although numerous papers on this subject have appeared in the French, Italian, Spanish, and Latin American literature,¹⁻³⁶ a careful search of the *Index Medicus* has revealed only one case report³⁷ in the English language. The syndrome appears to have attracted little attention from physicians in this country. Fishberg,³⁸ in his textbook, *Heart Failure*, refers to the syndrome and states that he has observed many necropsies which support Bernheim's views. White,³⁹ in the latest edition of his book, mentions the syndrome for the first time but expresses doubt on theoretical grounds, as to its entity.

The purpose of this paper, therefore, is to present our findings in three cases of Bernheim's syndrome, two of which were diagnosed during life and confirmed at necropsy and one discovered unexpectedly on post-mortem examination.

CASE REPORTS

CASE 1.—C. C., a 44-year-old Filipino seaman was first admitted to the U. S. Marine Hospital on Oct. 24, 1939, for treatment of asymptomatic hypertension which disqualified him for employment. His past history revealed that he contracted gonorrhea in 1928 and that he had had no other illnesses except the usual childhood diseases.

Examination revealed a well-developed and well-nourished adult male of small stature, in no acute distress. His temperature was 98.6° F., pulse, 94, and respirations, 18. The fundi showed disc margins which were clear and distinct. The retinal arterioles were tortuous and "silver-wire" in character. Arteriovenous notching was evident. There were no retinal hemorrhages or exudates. The radial pulses were of good volume, equal, and regular. The blood pressure was 234/142. There was engorgement of the cervical veins.

The apex impulse of the heart was 2.5 cm. outside the left mid-clavicular line in the fifth intercostal space. The sounds were of good quality and no murmurs were heard. The second aortic sound was loud and snapping. The lungs were resonant throughout. The breath sounds were vesicular in type and there were no râles. The liver and spleen were not palpable. There was no dependent edema. The circulation time (arm to tongue) was 19 seconds using decholin. The venous pressure was 160 mm. of water. Blood Wassermann and Kahn reactions were negative. Routine urine analysis showed specific gravity of 1.015 and a trace of albumin. X-ray of the heart revealed the maximum cardiac measurements as 5 cm. to the right and 10.5 cm. to the left; the transverse diameter of the chest was 28.4 centimeters. The lateral view showed obliteration of the retrocardiac space. Electrocardiogram revealed normal sinus rhythm with a ventricular rate of 86; P-R interval, 0.16 second; QRS interval, 0.08 second; slurred QRS in limb leads; T waves inverted in Leads II and III; and right axis deviation.

After one month's hospitalization, the blood pressure showed little change, and the patient was discharged. He was readmitted to the hospital on May 16, 1940, with the complaint of swelling of the abdomen and legs. There was no history of exertional or paroxysmal nocturnal dyspnea.

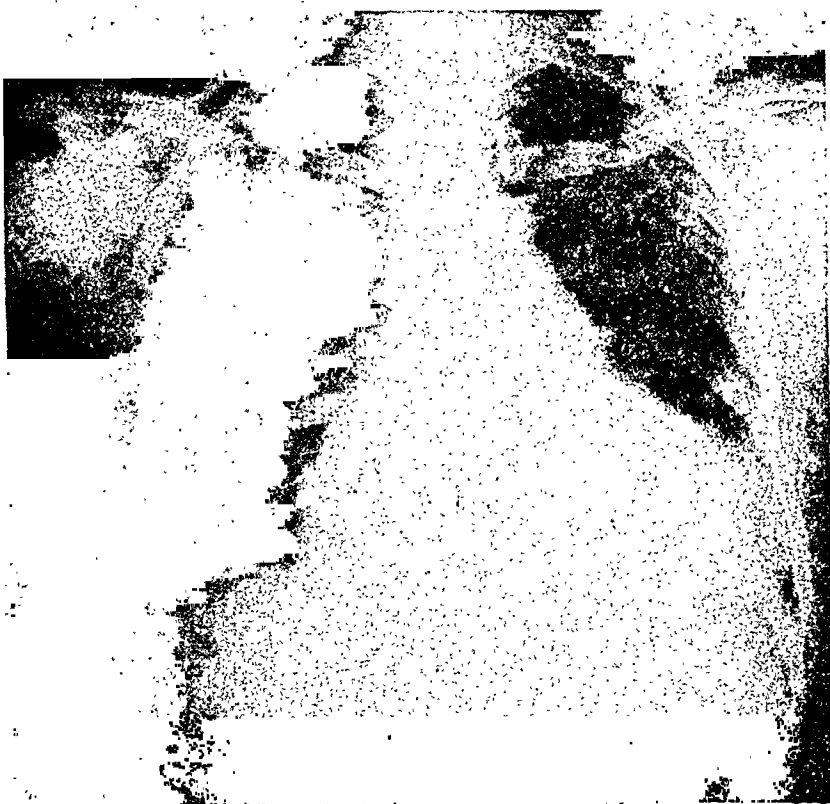


Fig. 1.

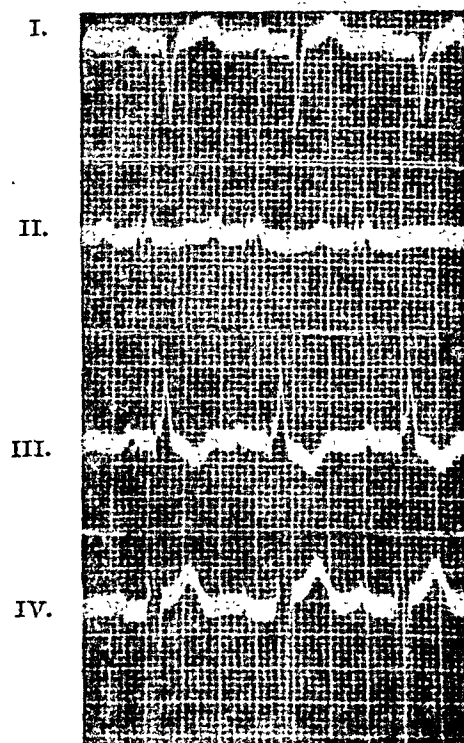


Fig. 2.

Fig. 1.—Case 1. Roentgenogram showing marked enlargement of the heart. Note the absence of pulmonary congestion.

Fig. 2.—Case 1. Electrocardiogram showing right axis deviation.

Examination revealed a blood pressure of 204/140. The left border of the heart was in the anterior axillary line. No murmurs were heard. The heart rate was 80 per minute and regular. Scattered rhonchi were present throughout the lungs. There was marked distention of the entire abdomen and a fluid wave was elicited. On percussion, there was dullness in the flanks as well as shifting dullness on change of position. There was moderate edema of the scrotum and marked pitting edema of the legs as high as the mid-thigh region. The arm-to-tongue circulation time was 20 seconds. Roentgenogram of the heart (Fig. 1) showed an appreciable increase in the transverse diameter of the cardiac silhouette as compared with that of the former admission. Maximum cardiac measurements were 5.6 cm. to the right and 12.4 cm. to the left; the transverse diameter of the chest was 27.5 centimeters. There was no evidence of pulmonary congestion. The electrocardiogram was essentially the same as on first admission showing right axis deviation and inversion of T waves in Leads II and III (Fig. 2). Urinalysis showed a specific gravity of 1.018 with no

abnormal findings. The blood picture revealed 3,500,000 red blood cells and 70 per cent hemoglobin. The nonprotein nitrogen of the blood was 46 mg. per cent; the total serum protein was 6.9 Gm. per cent; albumin was 3.5 Gm. per cent and globulin, 3.4 Gm. per cent. Icterus index was 15.

The patient was digitalized and 2 c.c. of Mercupurin were administered intravenously every three to four days. On this therapy together with fluid and salt restriction, dependent edema and ascites disappeared. At the time of discharge, on July 8, 1940, the blood pressure was 185/140, the pulse was 80 per minute, and there was no evidence of circulatory failure except for prominence of the cervical veins.

The patient was readmitted to the hospital Oct. 1, 1940, with the same complaint; namely, marked swelling of the lower extremities and abdominal distention. There was also slight dyspnea on moderate exertion. In the interval, he had been on a maintenance dosage of digitalis.

Physical examination revealed no evidence of dyspnea or orthopnea. The patient was able to lie flat in bed without respiratory distress. The lips were cyanotic. There was marked distention of the cervical veins. The heart findings were as formerly noted. Blood pressure was 200/140. There were no murmurs or thrills. The cardiac rate was 98 per minute and regular. There was marked prominence of the abdominal wall with eversion of the umbilicus. The liver border was 3 fingerbreadths below the right costal margin in the mid-clavicular line. A fluid wave was elicited in the abdomen and there was shifting dullness on change of position. There was scrotal edema and swelling of the lower extremities as high as the mid-thigh region. The arm-to-tongue circulation time was 25 seconds. The venous pressure was 180 mm. of water. X-ray of the heart showed no further change in cardiac size. There was still no evidence of pulmonary congestion. The electrocardiogram was as formerly noted. The total serum protein was 6 Gm. per cent with an albumin level of 3.4 Gm. per cent and a globulin level of 2.6 Gm. per cent.

Four thousand cubic centimeters of clear, yellow fluid were withdrawn by abdominal paracentesis. The maintenance dosage of digitalis was increased to $1\frac{1}{2}$ grains twice daily and 2 c.c. of mercupurin were given every two to three days. It was found that, in spite of the restriction of fluid and sodium, edema would develop rapidly if the mercurial diuretic was withheld for more than several days. Gain in weight was used as the indication for mercupurin therapy. The patient was maintained on this regime for seven months and was again discharged on a maintenance dosage of digitalis. He returned as an out-patient once each week for an injection of mercupurin but, after two months, had to be readmitted to the hospital because of a recurrence of symptoms.

Upon entering the hospital on June 3, 1942, there was no evidence of respiratory distress. Blood pressure was 182/136. The pulse was 96 per minute and regular except for an occasional ectopic beat. Cyanosis of the face was marked. The cervical veins were distended and pulsating. The heart was markedly enlarged to the left and there was a soft blowing systolic murmur at the apex as well as a protodiastolic gallop. The lungs were clear on auscultation except for a few moist râles at both bases posteriorly. There was marked protrusion of the abdomen. The liver was 3 fingerbreadths below the right costal margin in the mid-clavicular line. Marked pitting edema of the lower extremities and scrotum was present. The arm-to-tongue circulation time was 40 seconds using decholin. The venous pressure was 200 mm. of water. Roentgenogram of the heart showed marked enlargement in the transverse diameter and also toward the back. The maximum cardiac measurements were 6.8 cm. to the right and 10.8 cm. to the left; the transverse diameter of the chest was 25.3 centimeters. There was obliteration of the retrocardiac space. There was still no evidence of pulmonary congestion. Electrocardiogram showed normal sinus rhythm with a ventricular rate of 80; P-R interval, 0.21 second; QRS interval, 0.09 second; slurred QRS in limb leads; T waves diphasic in Lead II and inverted in Lead III; and right axis deviation.

The patient showed slight improvement at first on rest in bed and injections of mercupurin, but, after several months, his condition became steadily worse and dyspnea and orthopnea became evident. The latter symptoms thus appeared for the first time after three years of observation. At the same time, the systolic apical murmur increased in intensity and duration. Moist râles were heard at the lung bases posteriorly and x-ray of the chest revealed pulmonary congestion involving both lower lobes. Ascites and dependent edema persisted. The patient failed to respond to all measures and died on Oct. 2, 1942. The final medical impression was hypertensive heart disease associated with Bernheim's syndrome.

Autopsy.—*External Examination:* The body was that of a male adult Filipino of small stature. There was pitting edema of the ankles and legs. The abdomen was protuberant. The mucous membranes were pale and showed no evidence of icterus. There were no petechiae.

Internal Examination: The peritoneal cavity contained blood-tinged, yellow fluid amounting to approximately 3 liters. There were adhesions between the omentum and the anterior abdominal wall suggesting the healing of previous sites of paracenteses. The pleural cavities showed no free fluid present. There were no adhesions on the left side but a few fibrous attachments were found on the right. The pericardial cavity had a smooth lining with a content of about 25 c.c. of clear fluid. The heart was greatly enlarged, particularly to the left, and weighed 710 grams. A transverse section a short distance above the apex of the heart revealed a remarkable thickening of the interventricular septum which ranged from 2 to 2.5 cm. in thickness and which had a firm, resilient texture. The right ventricular cavity was encroached upon by this convex septal bulging. However,



Fig. 3.—Case 1. Transverse section of the heart showing marked hypertrophy of the left ventricle and the interventricular septum. The right ventricle is reduced in size by the bulging septum, the left ventricle by concentric hypertrophy.

the capacity of the right ventricle appeared to be about equal to that of the left, since the latter was markedly reduced by concentric hypertrophy of the myocardium (Fig. 3). There was a considerable area of fibrous replacement of the left ventricular wall, laterally, extending from the mid-portion to include the apex. Dissection of the coronary arteries showed that the left was predominant. The caliber was large. There were numerous atheromatous foci. Fresh thrombus could not be found. The valves of the heart showed considerable atheroma. The dimensions of the valves were: mitral circumference, 13 cm.; aortic, 6.5 centimeters. There was no evidence of old or recent vegetation, fibrosis, or calcification. The right auricle was considerably dilated. No thrombi were present. The aorta showed considerable thickening of the entire wall. There was no aneurysm. The intima showed longitudinal wrinkles and flat grayish-white foci suggesting syphilitic aortitis. The lungs were partially aerated and had a brownish-yellow color indicative of passive congestion. On section the tissue was moist and considerable hemorrhagic fluid exuded from all lobes. Small foci appeared to be recently consolidated. These were distributed centrally in both lungs. The liver weighed 1,100 grams. Its capsule was smooth, and, on section, the substance was yellow-brown and not unduly resistant. The principal vessels appeared normal. The spleen was not enlarged and showed normal markings.

Gastrointestinal Tract: Numerous areas of intense congestion were found in the stomach and small intestine. There was marked thickening and hemorrhagic infiltration in the descending colon for about 25 cm. suggesting thrombosis of the veins. The kidneys weighed 305 grams together and were of about equal size. On section each kidney showed a cortical width of about 7 millimeters. On stripping the capsule, the surface was left finely granular. In addition there were a number of small sunken and retracted areas of fibrosis.

Microscopic Examination.—The myocardial fibers were larger than usual. There was a moderate amount of interstitial connective tissue interrupting the muscle fibers over an extent of several low-power fields. Dilated capillary vessels were seen in the middle of these scars. Large branches of the coronary system were seen in section and showed very prominent atheromatous thickening of the intima and severe reduction of the lumen. The aorta showed numerous small scars in the media together with dilated capillary vessels and clusters of lymphocytes. There were also foci of vacuolization and lipoid deposit in the intima. The lungs showed marked congestion of the capillaries and veins throughout several sections. The alveolar spaces contained many large monocytes containing brown granular pigment. There were small areas of infarction. The general architecture of the liver was well preserved, the central areas were congested. Most of the glomeruli of the kidneys were well preserved, but a few scattered, partly or completely fibrotic glomeruli were noted. Numerous interstitial areas appeared fibrosed and moderately infiltrated by lymphocytes. The arteries showed severe thickening and hyalinization involving large and small branches. Necrosis of arterial walls could not be found. Pathologic diagnoses were: fibrosis of the myocardium; hypertrophy of the heart; coronary arteriosclerosis; nephrosclerosis; passive congestion of the lungs, liver, and kidneys; syphilitic aortitis; anasarca; and generalized arteriosclerosis.

CASE 2.—F. R., a 42-year-old Filipino merchant seaman was admitted to the hospital on Sept. 27, 1943, with a history of persistent swelling of the ankles since 1939, followed, a short time later, by shortness of breath on exertion. One week prior to admission he had some discomfort in the chest and because of this was referred to the hospital. The past history was essentially negative except for a Neisserian infection in 1918.

Physical examination revealed a well-nourished and well-developed male of small stature, not acutely ill. There was no evidence of dyspnea or orthopnea. Both pupils reacted to light and accommodation. The fundi showed marked tortuosity of the vessels and hyperemic discs. No hemorrhages were noted. The lungs were clear to percussion and auscultation except for a few fine râles at both bases. The heart was considerably enlarged with the left border in the anterior axillary line. There was a blowing systolic murmur at the apex. The aortic second sound was louder than the pulmonic. The cardiac rate was 114 per minute; the rhythm was regular. Blood pressure was 230/155. The liver edge was felt 3 fingerbreadths below the right costal margin in the mid-clavicular line. There was evidence of free fluid in the abdomen. There was moderate pitting edema of both ankles. The arm-to-tongue circulation time was 20 seconds using decholin. The venous pressure was 150 mm. of water. A diagnosis of hypertensive heart disease with Bernheim's syndrome was made. X-ray examination of the heart showed the cardiac shadow to be markedly enlarged (Fig. 4). The maximum cardiac measurements were 5.9 cm. to the right and 11.6 cm. to the left; the transverse diameter of the chest was 26 centimeters. A lateral study showed marked obliteration of the retrocardiac space by the left ventricle. Fluoroscopic examination revealed definite left ventricular enlargement but failed to show any evidence of right auricular dilatation. Electrocardiogram before the administration of digitalis, showed normal axis with inversion of the T waves in the limb leads (Fig. 5). Urinalysis showed a specific gravity of 1.010 with moderate albuminuria, many red blood cells, and a few hyaline and granular casts. The blood count was essentially normal. Wassermann and Kahn tests were negative. Nonprotein nitrogen was 60 mg. per cent. Total protein was 7.2 Gm. per cent with an albumin level of 3.3 Gm. per cent and a globulin level of 3.9 Gm. per cent.

While in the hospital the patient showed little evidence of dyspnea. There were a few moist râles at both lung bases. Moderate edema of the lower legs persisted. Patient was digitalized and given mercupurin intravenously once or twice weekly with some improvement. On Nov. 18, 1943, the blood pressure was 250/160. There was a loud systolic murmur and gallop rhythm at the apex. The heart rate was 80 per minute and the rhythm

was regular. The second pulmonic sound was markedly accentuated and considerably louder than the second aortic sound. The lungs showed many moist râles bilaterally. The circulation time, arm-to-tongue, was 65 seconds. The venous pressure was 270 mm. of water. Dyspnea and orthopnea were present. On Nov. 30, 1943, the patient developed a convulsive seizure lasting several minutes. Convulsions recurred in rapid sequence and the patient lapsed into coma and expired Dec. 4, 1943.

Autopsy.—*External Examination:* The body was that of a normally developed and fairly well-nourished oriental male of adult age. The mucous membranes showed no evidence of icterus. There were no petechiae.

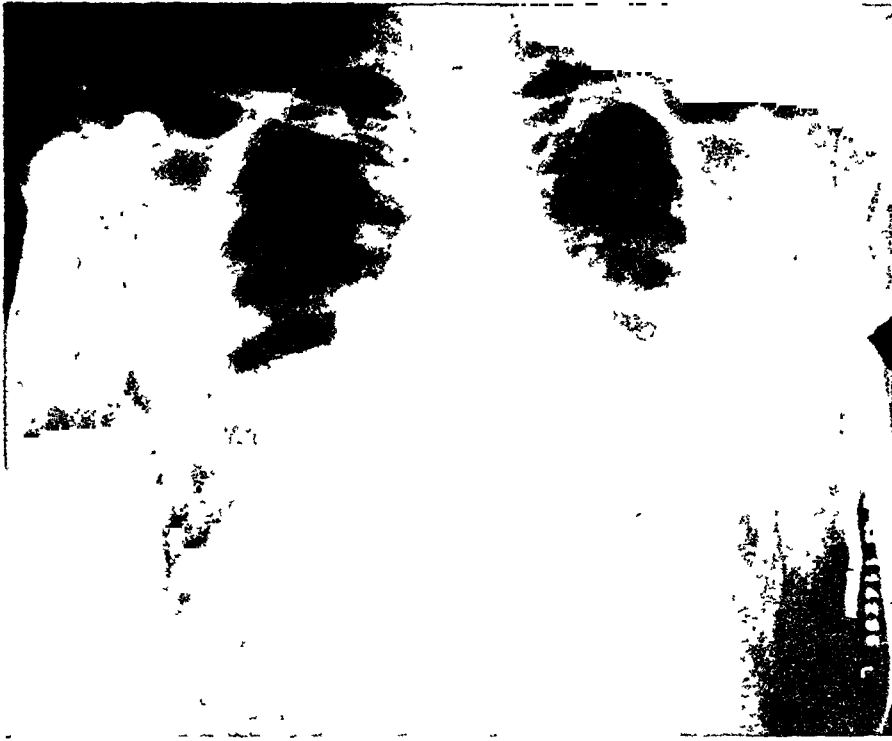


Fig. 4.

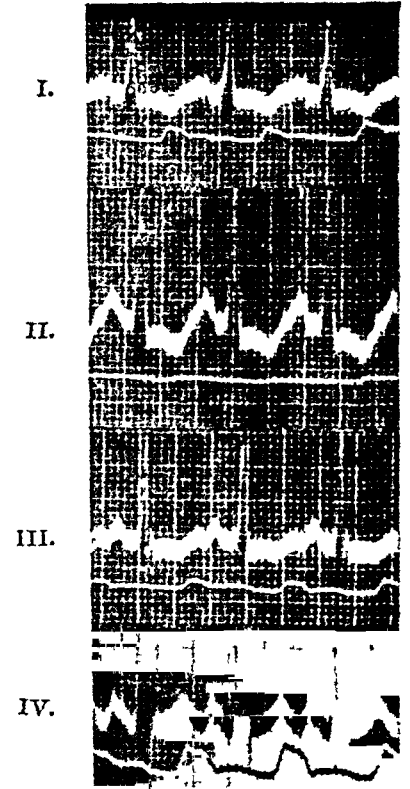


Fig. 5.

Fig. 4.—Case 2. Roentgenogram showing marked enlargement of the heart.

Fig. 5.—Case 2. Electrocardiogram showing normal electrical axis.

Internal Examination: The peritoneal cavity contained no free fluid or exudate. The pleural cavities showed a little free fluid present. There were no adhesions. The pericardial cavity was found to have a lining which was dull and fibrinous with no free fluid noted. The heart weighed 725 grams. The surface was fibrinous with hemorrhagic foci posteriorly. The myocardium was firm in consistency and showed no foci of softening or hemorrhage. The thickness of the left ventricle was 2.3 centimeters. The septum was 3 cm. thick. The right ventricular cavity was markedly compromised by the hypertrophied and bulging septum (Figs. 6 and 7). The coronary arteries showed patent orifices. On dissection they were patent and had many foci of atheroma and calcification. The endocardium showed no mural thrombi. The valves had normal surfaces. No vegetations were observed on any of the valves. The measurements were: tricuspid, 10 cm.; mitral, 9 cm.; pulmonary, 7 cm.; and aortic, 7.2 centimeters. The aorta showed slight patchy yellow discoloration and a few atheromatous plaques. The lung surfaces were smooth, and there was no exudate. On section, the tissue contained air in all portions and had a yellowish color. The liver weighed 850 grams. Its surface was smooth; it was firm in texture; and it was mottled in color. The spleen was not enlarged. On section its pulp was purple in color and firm in consistency. The kidneys were symmetrical and weighed 400 grams together. On section the cortex had a width of 7 millimeters. The capsule stripped readily, leaving a finely granular surface. The markings were unclear and the color was purple.

Microscopic Examination.—The large coronary trunks had thick hyaline walls with foci of lipid and lymphocytes. The epicardium was covered by red cells and fibrin in certain sections. The myocardial fibers were greatly enlarged and the nuclei huge. Some fibrosis was apparent. The glomeruli of the kidneys contained blood cells. There were

partly hyalinized and swollen areas especially close to the afferent artery or actually involving it. Peculiar blotchy hyaline necrosis thickened and occluded many arterioles. The larger arteries showed severe atheromatous changes. The centrilobular regions of the liver were heavily infiltrated by red blood cells. The arterioles showed necrotic hyaline areas. There were many pigment-laden phagocytes in the air spaces of the lungs. Many bronchioles were filled with polynuclear cells. Hyaline thrombi of the arterioles were noted. The pathologic diagnoses were: nephrosclerosis, malignant; diffuse arteriolitis; and hypertrophy of the heart, especially the septal portion of the left ventricle.

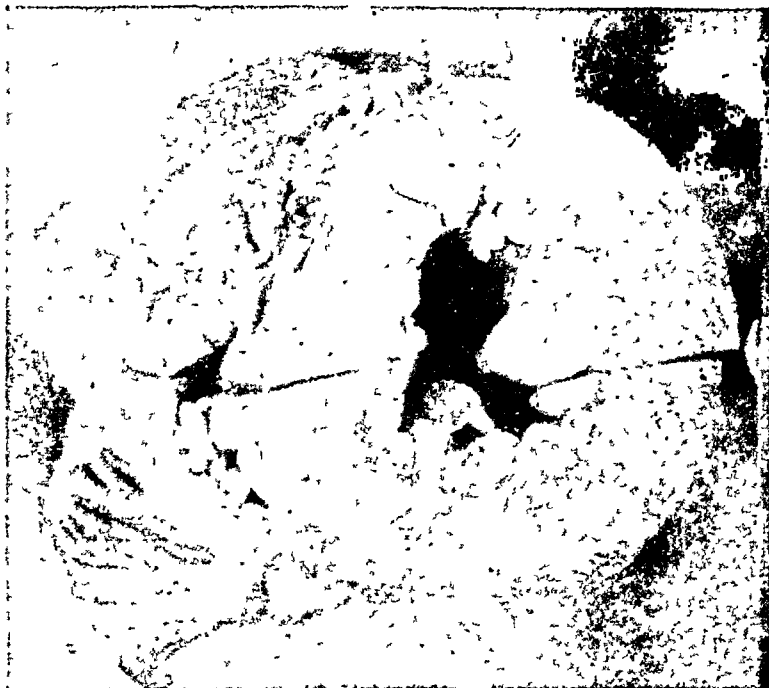


Fig. 6.—Case 2. Transverse section of heart (midway between apex and base) showing marked left ventricular hypertrophy. The cavity of the right ventricle is greatly reduced in size by the bulging interventricular septum which measures 3 cm. in thickness.

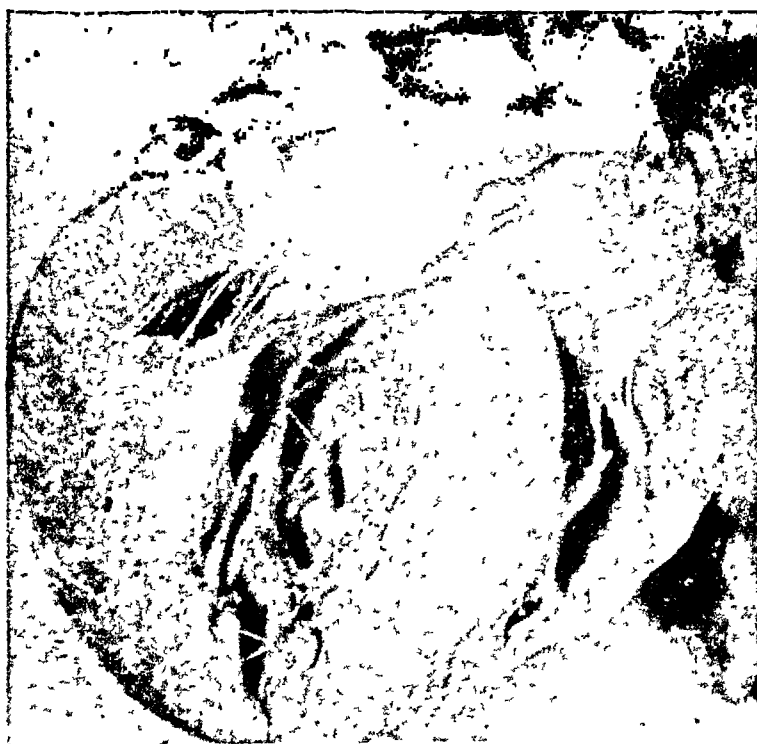


Fig. 7.—Case 2. Longitudinal section of the heart showing relative size of the ventricles. Note the bulging septum and the reduced capacity of the right ventricle.

CASE 3.—W. R., a 73-year-old white merchant seaman was admitted to the hospital on Sept. 22, 1943, with the complaint of dyspnea on exertion and swelling of the ankles of two months' duration. Two weeks prior to admission he experienced a severe attack of dyspnea requiring an injection of morphine. Past history was noncontributory. There was no previous history of rheumatic fever or syphilis.

Physical examination revealed an elderly white male not acutely ill. His temperature was 98.6° F., and his respirations, 20. The face and nail beds were cyanotic. The blood pressure was 130/80. There was marked distention of the cervical veins. The left border of the heart was 3 cm. outside the left mid-clavicular line. There was a loud, harsh, systolic murmur over the precordium with maximum intensity at the aortic area where a systolic thrill was palpated. The second aortic sound was absent. A mid-diastolic rumble was heard at the apex. The cardiac rhythm was irregularly irregular with an approximate ventricular rate of 88 per minute. The lungs were clear throughout; no râles were heard. The liver border was 4 fingerbreadths below the right costal margin in the mid-clavicular line. There was marked pitting edema involving the legs as high as the mid-thigh region. Large blebs containing clear fluid, were present over the lower legs. Blood Wassermann and Kahn reactions were negative. Routine urinalysis showed a specific gravity of 1.015 with negative findings. X-ray of the heart revealed the maximum cardiac measurements as 4.8 cm. to the right and 12.6 cm. to the left; the transverse diameter of the chest was 33.2 centimeters. There was evidence of small infarcts in the right lung base adjoining the heart (Fig. 8). The lateral view showed calcification in both the mitral and aortic valve rings. Electrocardiogram revealed auricular fibrillation with a ventricular rate of approximately 60; diphasic T waves in the limb leads due to digitalis effect; and normal axis (Fig. 9).



Fig. 8.—Case 3. Roentgenogram showing marked enlargement of the heart. Note absence of pulmonary congestion. There are small infarcts at the right lung base.

The clinical diagnosis was rheumatic heart disease, mitral and aortic stenosis, auricular fibrillation, and congestive heart failure. The patient was digitalized and was given mercupurin intravenously twice weekly. While in bed he manifested little dyspnea but continued to show the signs of marked right heart failure. He was discharged on Jan. 14, 1944, for continued rest in bed at home.

The patient was readmitted on Feb. 17, 1944, with the complaint of marked swelling of the lower extremities which were covered with "blisters" in their lower parts.

Examination revealed similar findings as on previous admission. Cyanosis was marked. There was engorgement of the cervical veins. Moist râles were heard at both lung bases posteriorly. The abdomen was distended and a fluid wave was elicited. There was marked pitting edema of both lower extremities as high as the groin. Large weeping ulcers were present over the middle two-thirds of both tibiae.

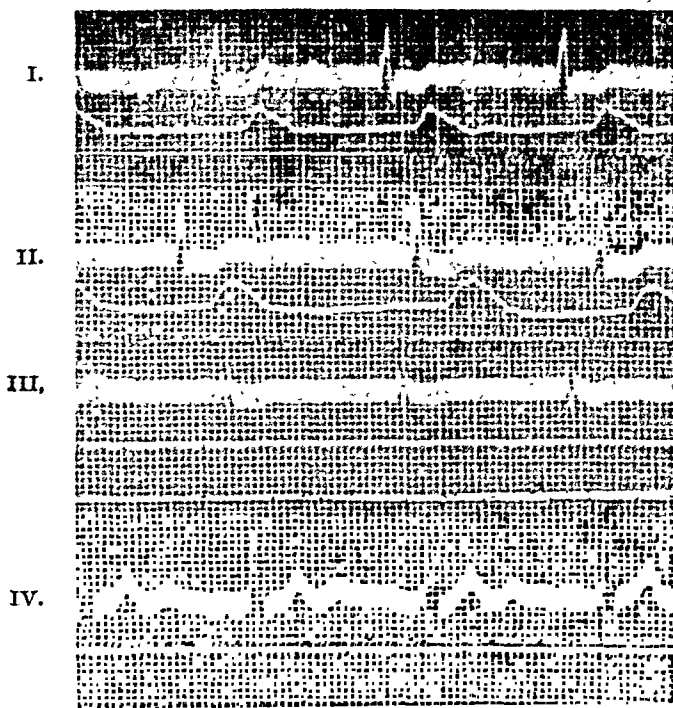


Fig. 9.—Case 3. Electrocardiogram showing normal electrical axis.



Fig. 10.—Case 3. Transverse section of the heart (midway between apex and base). Note convex bulging of the septum which measures 3.2 cm. in thickness. The right ventricle is markedly reduced in size.

On rest in bed, digitalis, and mercupurin, slight improvement ensued. Later, the patient became drowsy and appeared dehydrated. A blood nonprotein nitrogen was found to be 138 mg. per cent. All further measures failed to influence the course of the illness, and the patient expired on March 19, 1944.

Autopsy.—*External Examination:* The body was that of a well-developed and well-nourished white man of advanced age. There was pitting edema of the legs. The mucous membranes showed no evidence of icterus. There were no petechiae.

Internal Examination: The peritoneal cavity had some free fluid but no exudate. There were no adhesions. The pleural cavities showed smooth surfaces and a little free fluid was present. The pericardial cavity had a smooth lining and contained about 25 c.c. of clear fluid. The heart weighed 800 grams. The myocardium was firm in consistency and showed a few foci of flattening and retraction, especially in the right ventricle. The left ventricle measured 2.6 cm. in thickness. The interventricular septum bulged convexly toward the right, markedly encroaching upon the right ventricular cavity. The septum measured 3.2 cm. in thickness (Fig. 10). The coronary arteries showed small orifices. On dissection they were patent and had many foci of atheroma and calcification. The endocardium of the auricles showed friable pink mural thrombi. The valves had normal surfaces and tendons on the right side of the heart. The mitral curtains and tendons were short and adherent. There was marked deformity of the mitral and aortic valves with abundant knoblike calcified encrustations in the sinuses of Valsalva, holding the aortic orifice in a closed position.

The lung surfaces were dull and showed a fibrinous exudate. On section the tissue contained air in all portions except for large wedges of dark red consolidation sharply outlined and present in all lobes on both sides. The liver weighed 1,520 grams and showed a finely nodular surface. Its texture was firm and its color brown gray. The spleen was of normal size and on section its pulp was firm. The kidneys were about equal in size and weighed about 390 grams together. On section the cortex had a width of 6 millimeters. The capsule stripped easily, leaving a smooth surface. The markings were clear with a few small cysts and a rare zone of yellowish color with a reddened margin.

Microscopic Examination.—The myocardium showed considerable interstitial fibrosis. Many of the muscle fibers were enlarged. There was hyalinization with foci of calcification in the base of a valve. A few cellular foci were noted near blood vessels and beneath the endocardium. They consisted of large cells with ovoid nuclei. Some pigment was present. Large areas of necrosis and monocytic infiltration were noted in the wall of an auricle. Its lumen was occupied by a fibrin thrombus with masses of leucocytes and red blood cells enclosed. A large branch of the pulmonary artery had a degenerated edematous and fibrinoid wall with destruction of the endothelium. The lumen was filled by a thrombus of fibrin and blood cells with large central areas of laking. The small arteries of the lung also contained thrombi and showed foci of atheroma, edema, lamellar splitting, and monocytic infiltration. The alveoli contained a great many pigment-filled monocytes. The centrilobular areas of the liver were severely damaged and infiltrated by red blood cells. About half of the trabeculae were thus involved. Many phagocytes and some fibroblasts were noted. The arteries of the kidney were thick and hyaline. The great majority of the glomeruli and tubules appeared intact. Pathologic diagnoses were: rheumatic endocarditis with mitral and aortic stenosis; mural thrombosis of the auricles; pulmonary infarctions; arteriosclerosis of the pulmonary arteries; and central necrosis of the liver.

DISCUSSION

The advent of systemic venous engorgement as the first sign of circulatory embarrassment and its persistence in the absence of pulmonary congestion, suggested the clinical diagnosis of Bernheim's syndrome in Cases 1 and 2. Although ascites, enlargement of the liver, and dependent edema existed for some time, roentgenograms of the chest as well as physical signs failed to reveal evidence of pulmonary congestion until a later stage. The patients, moreover, were able to lie flat in bed and to engage in slight to moderate activity without manifesting respiratory distress. Correlated with these features of the clinical picture was the interesting observation in the early stage of the disease, of an elevated venous pressure with a comparatively normal arm-to-tongue circulation time. Interference with the filling of the right ven-

tricle, therefore, seemed more competent to explain these findings than did failure of this chamber following left ventricular insufficiency. Furthermore, if the engorgement of the systemic veins had had its pathogenesis in true insufficiency of the right ventricle, an appreciable dilatation of that chamber should have been noted. On the contrary, necropsy study revealed no dilatation of the right ventricle in spite of long standing symptoms of right heart failure. This finding, together with the marked displacement and bulging of the interventricular septum into the right ventricle, lends support to Bernheim's contention that interference with the filling of the right ventricle underlies systemic venous engorgement in these cases.

The development of pulmonary congestion as a terminal event in this syndrome, has been a subject of considerable discussion. In Case 1, a loud, blowing apical, systolic murmur and gallop rhythm developed with the onset of pulmonary congestion late in the course of the disease. In Case 2, gallop rhythm and marked accentuation of the second pulmonic sound similarly preceded the development of bilateral basal râles and orthopnea. It appears, therefore, that prior to these findings the clinical picture was dominated by signs and symptoms arising from obturation of the right ventricle; whereas, left ventricular failure, if it existed at all, was either minimal or neutralized by diminished right ventricular output. The normal circulation time and increased venous pressure in both cases, strengthen this view. With the appearance of gallop rhythm and relative mitral insufficiency, congestion of the lungs soon developed as a result of failure of the left ventricle.

In Case 3 in which the cardiac lesions were aortic and mitral stenosis, the anatomic features of Bernheim's syndrome were discovered unexpectedly at necropsy. In retrospect, the only unusual feature was the extreme degree of "right heart failure" associated with minimal pulmonary congestion. Inasmuch as a similar clinical picture is sometimes seen in mitral stenosis with failure of the right ventricle, no other mechanism was suspected. The discovery of a greatly reduced right ventricular chamber at autopsy was, therefore, an interesting paradox.

Certain electrocardiographic findings have been described as characteristic of Bernheim's syndrome. Some authors have stated that left ventricular preponderance is the usual feature of the electrocardiogram. From anatomic considerations, one would indeed anticipate rotation of the electrical axis of the heart to the left; nevertheless, in none of the three cases which we have presented, was this finding observed. On the contrary, there was right ventricular preponderance in Case 1 and a normal electrical axis in Cases 2 and 3. Glushein and Geer³⁷ similarly reported "no axis deviation" in the case which they observed. These seemingly paradoxical findings require explanation in view of the marked difference in the relative size and thickness of the respective ventricles. Inasmuch as Eliaser and Konigsberg⁴⁰ found right axis deviation in 40 per cent of their cases of cardiac aneurysm, Rowland⁴¹ regards right axis deviation in association with left ventricular enlargement as suggestive of this diagnosis. Klainer,⁴² in a recent report, found only thirty-six instances of right axis deviation in hypertensive or arteriosclerotic heart disease in all the electrocardiographic records of the Beth Israel Hospital over a ten-year period. He attributed the right axis deviation to widespread necrosis of the left ventricle which nullified the effects of hypertrophy of this chamber. It also seems possible, however, that a bulging and deviated interventricular septum, as seen in the syndrome of Bernheim, may alter the electrical axis of

the heart and even be responsible for unexpected right axis deviation in hypertensive heart disease.

Dulcos²⁸ regarded the kymographic demonstration of right auricular dilatation as a valuable diagnostic sign when Bernheim's syndrome is suspected in a case with left ventricular enlargement. Glushein and Geer³⁷ similarly believe that the fluoroscopic findings, as observed in their case, are almost pathognomonic of the syndrome of Bernheim. The combination of a large left ventricle with a large right auricle, the two other chambers being of normal size, is not found, according to these authors, in the ordinary types of heart disease. In our first case, fluoroscopic studies seemed to confirm the clinical impression of Bernheim's syndrome. In Case 2, however, right auricular enlargement could not be established fluoroscopically or by kymographic studies.

Case one provided an opportunity of studying the syndrome of Bernheim from the presymptomatic stage to death, a period of three years. Our observations are, for the most part, in accord with the description of the clinical picture recorded by Mazzei.¹¹ In the first or anatomic period, there are few or no important clinical signs. Interference with the filling of the right ventricle is counterbalanced by dilatation of the infundibular portion of the chamber and by enlargement of the right auricle. There may be some distention of the cervical veins and the venous pressure may be found elevated while the circulation time remains at the upper limit of normal. The second or clinical period, is divided into two stages. In the first stage, there is "dissociated" failure of the circulation; that is, systemic venous engorgement without disturbance in pulmonary blood flow. The lung bases are clear, and dyspnea is absent or minimal while hepatic enlargement, ascites, and dependent edema may be marked. During this interval, the circulation time may still be within upper normal limits or slightly increased while there is appreciable elevation in venous pressure. Fluoroscopic and kymographic studies may establish enlargement of the left ventricle and right auricle with normal size of the two other chambers. It is this stage of "isolated right heart failure" which is recognizable clinically as Bernheim's syndrome. In the second stage, which represents total failure of the heart, disturbance of the lesser circulation is added to the earlier symptoms of venous obstruction. It is at this time that dyspnea and orthopnea become evident. Regarding pathogenesis, however, our findings support the view of Martini and Joselevich¹⁷ that the terminal appearance of pulmonary congestion indicates failure of the left ventricle, and not the right ventricle as supposed by Mazzei.

From cases thus far reported in the literature, it appears that Bernheim's syndrome may develop in any condition capable of producing marked left ventricular hypertrophy and dilatation such as hypertension, arteriosclerosis, chronic nephritis, and aortic and mitral valvular disease.

SUMMARY AND CONCLUSIONS

1. The syndrome of Bernheim is a distinct clinical entity characterized by systemic venous engorgement without pulmonary congestion.
2. This picture of "isolated right heart failure" is the result of stenosis of the cavity of the right ventricle through displacement of the interventricular septum due to marked enlargement of the left ventricle.
3. The diagnosis is suggested when a patient with left ventricular hypertrophy shows signs of right heart failure as the first indication of circulatory embarrassment.

4. The "right heart failure" is not due to myocardial weakness but results from obstruction to blood flow through the right ventricle.

5. Dyspnea and other signs of pulmonary congestion are conspicuously absent or minimal until the terminal stage of the disease when failure of the left ventricle finally supervenes.

6. In a typical case, the circulation time may remain within normal limits for some time while the venous pressure is appreciably elevated.

7. Fluoroscopy may be helpful in demonstrating enlargement of the left ventricle and right auricle with normal size of the other two chambers.

8. The bulging and thickened interventricular septum may influence the electrical axis of the heart and even be responsible for unexpected right axis deviation in cases of left ventricular hypertrophy.

9. The syndrome of Bernheim may occur in any condition causing marked left ventricular hypertrophy and dilatation.

10. Three cases of this syndrome are presented in two of which the diagnosis was made during life and confirmed at necropsy while, in the third, the condition was discovered unexpectedly at post-mortem examination.

The authors wish to express their thanks to Dr. William H. Gordon for some of the essential data in Case 1 and to Dr. Lawrence Sophian, who performed the post-mortem examination.

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PERIPHERAL VASCULAR CHANGES IN DERMATOMYOSITIS

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IN THE differential diagnosis of occlusive diseases of the arterioles, one does not ordinarily think of so-called dermatomyositis. In the nomenclature¹ published by the Nomenclature Committee of the Section for the Study of the Peripheral Circulation of the American Heart Association, no mention is made of dermatomyositis, although such diseases as periarteritis nodosa and lupus erythematosus disseminatus are listed. Herrmann² in a recently revised textbook on diseases of the heart and arteries omitted dermatomyositis entirely. In a lengthy review³ of this textbook, appearing in the *Archives of Internal Medicine*, the author is specifically taken to task for this omission.

There may be several reasons for the omission of dermatomyositis in the classification of vascular diseases. First, dermatomyositis is a rare disease and frequently goes unrecognized.^{4, 5} Secondly, there seems to be a lack of unanimity as to just what dermatomyositis represents. Clinically, dermatomyositis, scleroderma, disseminated lupus erythematosus, the Libman-Sacks syndrome, and polyarteritis nodosa appear at times related, and the question has been raised whether or not there is a common denominator in all these

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vaguely understood diseases.^{7, 8} Finally, the term dermatomyositis is misleading. In standard textbooks of medicine^{9a, b} the disease may be found listed under such a heading as nonsuppurative myositis. Theoretically, the term dermatomyositis is applicable to any disorder in which there is inflammation of the muscles associated with skin changes. O'Leary and Waisman⁴ point out, however, that cutaneous manifestations may be totally absent. It appears that the cutaneous and muscular features of dermatomyositis have been unduly emphasized. In certain patients, the peripheral vascular changes dominate the entire clinical picture. Jager and Grossman⁵ observed a history of Raynaud's phenomena in four out of their nine reported cases of dermatomyositis. The following case report illustrates the pronounced peripheral vascular features of this illness.



Fig. 1.—Photograph showing trophic ulcer of left middle finger.

CASE REPORT

L. J., a 35-year-old, white, Jewish soldier, was in good health until May, 1943, when he developed a vesicular and papular type of eruption of his hands and feet. At the time he was stationed in a Southwest Pacific Area and was cared for by the staff of a station hospital unit. He was told he had a fungus infection and various local applications, including sulfonamides, were tried with periodic relief. About the time of the onset of his skin condition, he gradually developed weakness, abdominal pain, vague aches and pains in most of his muscles, cramps in his legs on walking and "nervousness." His appetite was poor, and he lost 25 pounds in weight. In March, 1944, the condition of his skin was much improved, but he developed an ulcer at the tip of the middle finger of his left hand. This ulcer was refractory to treatment. He was finally evacuated to the United States with a diagnosis of dermatitis of unknown origin and psychoneurosis.

Physical Examination.—The patient was well developed but undernourished and appeared chronically ill. The skin over the distal portion of his lower extremities had a slight gloss and seemed slightly adherent to the underlying structures. The palms and soles showed a few vesicles and some scaling, with evidence of atrophy. The left middle finger, at its distal volar aspect, showed an indolent-appearing ulcer. The ulcer had a necrotic slough over its base. There was tenderness over most of the large muscles, including the deltoid, trapezius, and triceps. Both hands and feet felt unusually cold, and in the dependent position there was marked rubor. The dorsalis pedis pulsations were not elicited, but the posterior tibial, popliteal, and radial pulsations were easily palpated. The left radial pulsation felt weaker than the right. Elevation of the lower extremities for a period of three minutes caused the feet to take on a blanched, cadaverous appearance. The heart and lungs were normal; the blood pressure measured 116/80; the spleen was not palpable, but there was moderate generalized lymphadenopathy. The reflexes were normal, but slightly hyperactive. Examination of the peripheral nerves by electrical stimulation showed spotty and irregular changes of both sides of the body. These changes did not appear to be organized in any special nerve distribution but occurred rather in a pattern referable to terminal motor branches. An oscillographic study revealed no pulsation over the dorsum of each foot and relatively less of a pulsation in the left wrist (Table I).



Fig. 2.—Photograph showing same indolent ulcer after six weeks of conservative treatment.

Laboratory Studies.—There was no anemia. The leucocyte count varied from 12,000 to 17,000 per cu.mm. The differential count was normal except that the monocytes occurred in a proportion of from 6 per cent to 12 per cent. The sedimentation rate was 15 mm. in one hour (modified Cutler method used; normal less than 10); the urinalysis was negative; the blood Kahn test was negative; blood smears for malaria were negative; a stool examination for parasites was negative; the blood cholesterol was 270 mg. per 100 c.c.; creatinine, 1.37 mg. per 100 c.c.; blood calcium, 10.4 mg. per 100 c.c.; total serum protein, 6.6 Gm.; globulin, 2.4 Gm. and albumin, 4.2; albumin-globulin ratio, 1.7; urinary creatine and creatinine studies revealed a creatine value of 112 to 51 mg. in 24 hours and a creatinine value varying from 1.56 to 1.52 Gm.; basal metabolism, -1 per cent; skin test for trichiniasis, negative; electrocardiograms, negative; x-ray of heart and lungs, normal; x-ray of left middle finger showed early atrophy of bone in the distal phalanx. X-ray examination of both feet was negative. No calcification was seen.

TABLE I. OSCILLOMETRIC STUDY

	RIGHT	LEFT
Calf	5.00	5.00
Ankle	1.80	1.90
Foot	0.00	0.00
Wrist	1.90	1.50

Biopsy.—A biopsy of the lymph node taken from the left epitrochlear region, on the same side in which the ulcer of the finger was located, showed evidence of inflammation. Several of the vessels in the surrounding tissue showed almost complete occlusion. Biopsies of the left soleus and the left deltoid muscles showed an increase in the nuclei of the sarcolemma. Here and there the bundles were covered with a few round cells, an occasional neutrophile, and a phagocyte. The interstitial stroma was infiltrated with plasma cells, small round cells, and occasional neutrophiles and phagocytes. The capillaries were surrounded by small round cells and plasma cells, and diapedesis was present. The walls of the medium sized vessels occasionally were infiltrated with round cells. There was no evidence of endothelial proliferation. The pathologist concluded: "There is a myositis with some muscular degeneration and atrophy, and there is a vascular disturbance, especially noted in the capillaries and smaller vessels" (Figs. 4, 5, and 6).



Fig. 3.—Photograph showing beginning trophic changes of the large right toe.

Course.—The patient was observed for approximately two months at this general hospital, during which time his chief complaints were generalized pains and aches, particularly in the lower extremities after walking, a nonhealing ulceration of the left middle finger, and progressive weakness. Writing a simple letter was enough to tire him. He was afebrile except for three episodes of fever lasting less than two days. Each bout of fever reached 100.5° F. Prior to hospitalization he was a heavy smoker, averaging two packages of cigarettes a day. This habit was discontinued after much persuasion. The ulcer on the finger was followed by the surgical service. Local applications of a bland ointment, together with physiotherapy, were prescribed. In the last five weeks the ulcer showed a tendency toward healing. Modified Buerger's exercises were given daily, but there was no appreciable improvement in the circulation of his lower extremities. A paravertebral block on the left side was performed. The



Fig. 4.—Photomicrograph of low-power magnification illustrating muscular degeneration. Note interstitial infiltration with plasma cells and phagocytes. Arrow indicates perivascular cuffing. Section from soleus muscle.



Fig. 5.—Photomicrograph of low-power magnification of a section from the deltoid muscle. Arrow points to small round-cell infiltration in muscle bundles.



Fig. 6.—Photomicrograph of high-power magnification illustrating the small round cell perivascular infiltration.

left lower extremity became warmer but there was no increase in the oscillometric readings. A brachial block was also tried on the left side. The left hand became warmer and there was definite relief of discomfort in the ulcerated finger. He was seen by the ophthalmologist who found narrowing of all the retinal arteries. The patient, however, had no complaints referable to his eyes.

DISCUSSION

Clinically, the peripheral vascular manifestations in this patient were similar to those seen in thromboangiitis obliterans. He was in the relatively young age group, of Jewish blood, and smoked excessively. The pathologic findings, however, revealed none of the endothelial changes characteristic of this disease. Periarteritis nodosa is suggested by the mild leucocytosis, the occasional bouts of fever, and the widespread and varied distribution of the clinical findings. Again, the pathologic findings were not characteristic of the usual case of periarteritis nodosa. The changes in the walls of the blood vessels seemed more in the nature of an infiltration without the necrosis seen in periarteritis. A skin biopsy taken from the region where the epitrochlear gland was removed showed no significant findings. Specimens taken from widely separated muscles, however, showed unequivocal evidence of a myositis such as has been reported in dermatomyositis (Fig. 4). Of particular interest are the pathologic changes seen in the arterioles (Figs. 5 and 6). The concept that dermatomyositis may be primarily a disturbance of the blood vessels was first proposed by Lépine,⁹ in 1901. The term "angiomyositis" was suggested. Certainly, the clinical course and manifestations of our patient lend support to the concept that dermatomyositis is primarily a vascular disease.

SUMMARY

1. A patient with certain features of so-called dermatomyositis is presented who showed pronounced peripheral vascular disturbances.

2. The widespread vascular changes in dermatomyositis are emphasized. In the differential diagnosis of occlusive diseases of the arterioles, so-called dermatomyositis should be included.

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THE RECRUIT'S HEART

REDUPLICATION OF THE FIRST SOUND: HEART STRAIN AND A NEW METHOD OF CALIBRATION

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I PUBLISHED a preliminary report on this subject in 1940, and I have since made a systematic examination of a further number of hearts in an endeavour to learn the significance of reduplication of heart sounds and the effect of strain on the heart. I have again, largely, made use of the hearts of young people, for they react more quickly and delicately to sudden strain. This has proved to be a fertile field which may stimulate and encourage other workers to improve on my results.

It is not my intention to deal with the bibliography of the subject of added heart sounds. I would refer those who are interested to a recent valuable paper by Evans, "Triple Heart Rhythm."² Moreover, I have to a certain extent followed Evans' schematic pattern when illustrating the cardiac cycle (Fig. 1).

I first drew attention in 1919 to the fact that reduplication was much more common in young children than in adults. Cossio and Braun-Menendez⁴ (1935) gave the following percentages: infants, 12 per cent; adolescents, 7 per cent; and adults, 1 per cent.

Many are the theories, which have been advanced in an effort to explain the mechanism producing added sounds, and Pillsbury⁵ points out that they are as variable as possible. Whilst most of the explanations have dealt with asynchronism of the closure of the aortic and pulmonary valves, Obrastzow⁶ (1905) states it indicates the beginning of cardiac degeneration, and Core⁷ (1912), dealing with mitral stenosis, suggests that audibility of the opening of the mitral valves is an explanation of double second sounds. Lian⁸ (1934) says that reduplication of the second sound and the third heart sound are two distinct phenomena; White⁹ (1939) associates accentuation of the third heart sound with exercise and dilatation of the left ventricle, whilst Sabathie¹⁰ (1938) refers to respiration, hypertension, and ventricular asynchronism as being important factors. One of the objects of this paper is to try to prove that reduplication *after exercise* is never of the second sound, but always of the first sound, and that it is due to asynchronism of ventricular contractions brought on by dilatation of the right ventricle.

RELATIONSHIP OF YOUTH AND REDUPLICATED SOUND

I (1940) have described elsewhere the systematic examination of the hearts of young subjects in the presence of other doctors, who can confirm the results. Briefly, the subjects consisted of a group of seventeen children between the ages of 6 and 8 years, a group of nine children between the ages

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of 8 and 10 years, and a group of twenty children between the ages of 10 and 12 years. Subsequently a group of R.A.F. recruits were examined at Halton; nine were nonathletic, untrained recruits and twenty-two had undergone mild training. Lastly, a group of twenty-one Home Guards were examined.

On analysis I found that 72 per cent of children between the ages of 6 and 12 years have reduplication of sounds either at rest or after exercise. In boy cadets between the ages of 14 and 20 years, 29 per cent had reduplication either at rest or after exercise. In R.A.F. recruits between the ages of 17 and 39 years, who had only mild training, the percentage had dropped to 19 per cent. Finally, among the Home Guards, after the age of 40 years, the percentage had dropped to nil.

I am of the opinion that, provided the exercise be severe enough, a change of rhythm can be induced in the hearts of most children under the age of 10 years.

Reduplication of First Sound After Exercise.—As already mentioned the hearts were examined in the presence of other doctors. I was puzzled by the fact that they were unable to hear the reduplication and to confirm my findings, until I noticed that they listened at the base, whereas I unconsciously listened over the apex. I afterwards found that I myself was unable to pick up the reduplication at the base.

Systole	Diastole	Systole	Diastole	
LUP	DUP	LUP	DUP	Normal rhythm at rest
LUP 1	DUP lup 2 r	LUP 1	DUP lup 2 r	Group 1 after exercise
lup LUP r 1	DUP 2	lup LUP r 1	DUP 2	Group 2 after exercise

Fig. 1.—Diagram showing position of reduplication of first sound in cycle in the two groups after exercise. *r*, reduplicated sound.

Let us consider the heart sounds from an onomatopoeic standpoint (Lup being the first sound and Dup being the second sound). On lying down, immediately after exercise, not only is a reduplication noticeable, but more often than not, a systolic "whiff" can be heard synchronizing with the Lup, or first sound. The other two sounds will therefore be the true second sound and the reduplicated sound (but not necessarily in that order). Having identified these sounds, if the stethoscope be then slowly slid, without lifting, from apex to base, it will be found that the reduplicated sound becomes more and more indistinct and disappears as the base is approached. The true second sound, on the other hand, becomes more and more audible and distinct towards the base. Although I and others have searched systematically on innumerable occasions, we have never yet been able to hear two distinct Dups at the base, as a result of exercise in these young hearts. I have come to the conclusion that what I had previously deemed to be a reduplicated second sound, is in fact reduplication of the first sound, and that it is a ventricular phenomenon, and has nothing to do with the second sound.

In certain boxers who have broken down in training, it has been found, after a period of rest, that the rhythm has changed from Group 1 to Group 2, only to change back again after resumption of training.

In short the sounds after exercise are Lup Dup lup or lup Lup Dup never Lup Dup dup. Tables I, II, and III should suffice for purposes of comparing and contrasting the old and the young.

These and other tables show that reduplication can easily be induced in young people; that the younger the subject the more easily it can be induced; that it can be brought on by exercise; that it becomes more noticeable on lying, but, on the other hand, when the subject is in the knee-elbow or prone position, or in the erect position, it becomes more indistinct. The reduplication should be sought for most diligently and carefully during the first few beats after exercise, for like the presystolic murmur of early mitral stenosis it may be evanescent and elusive.

Dilatation of the Heart After Exercise.—Thirty teleroentgenograms of the hearts of children were taken immediately before and after exercise. These were traced and charted. The charts were measured by means of an instrument

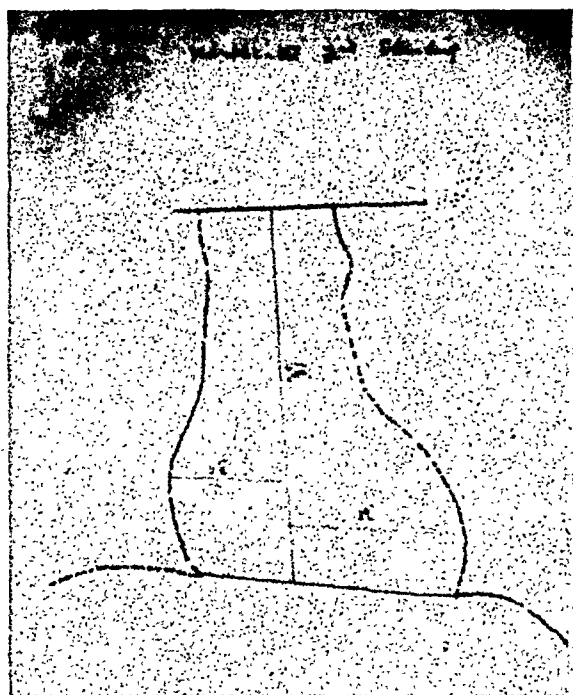


Fig. 2.

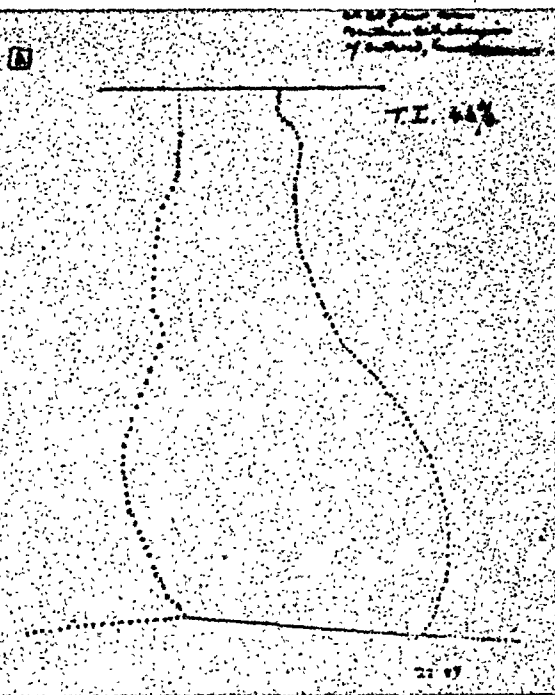


Fig. 3.

Fig. 2.—Chart of Public School boy boxer, aged 16 years, heavy weight. Area: 23.08 square inches.

Fig. 3.—Chart of Canadian champion, aged 20 years, featherweight. Area: 22.87 square inches.

TABLE I

AGE (YRS.)	REDUPLICATION ON LYING	REDUPLICATION ON LYING AFTER EXERCISE	REDUPLICATION STANDING AND PRONE POSITION	DURATION AFTER EXERCISE
7	0	0	0	0
7	0	+	0	Disappeared in 30 seconds
6	+	+	+	Persisted indefinitely in recumbent position
7	+	+	0	Persisted indefinitely in recumbent position
7	0	+	0	Disappeared in 30 seconds
7	0	+	0	Disappeared in 20 seconds
7	0	+	0	Disappeared in 30 seconds
7	0	+	0	Disappeared in 30 seconds
9	0	+	0	Present for first few beats only
9	Waxing and waning with respiration	+	0	Waxing and waning with respiration indefinitely

known as a *planimeter*, and the sectional areas in square inches were calculated down to two decimal places. The increase in the sectional area after exercise was found to be 8.75 per cent. (The subjects each did fifty skips.) Other interesting figures were obtained, as for example the heart of a child increases by about 1 square inch per year (some of these children have been x-rayed at yearly intervals). The area of the heart of a child of 10 years is, on the average, about 12 square inches, whereas the area of the heart of a boxer aged 22 years averages about 22 square inches. The heart of Kilrain, an old champion, aged 75 years, who fought Fitzsimmons, was 28.07 inches (Fig. 5).

That the right side of the heart is the first to dilate after exercise can be shown as follows. Each diagram was divided by a median vertical line running down the vertebral spines (Figs. 2, 3, 4, and 5). In this way a constant division of the heart into right and left sides was obtained, and it was found that the areas of the right sides of these hearts after exercise had increased by

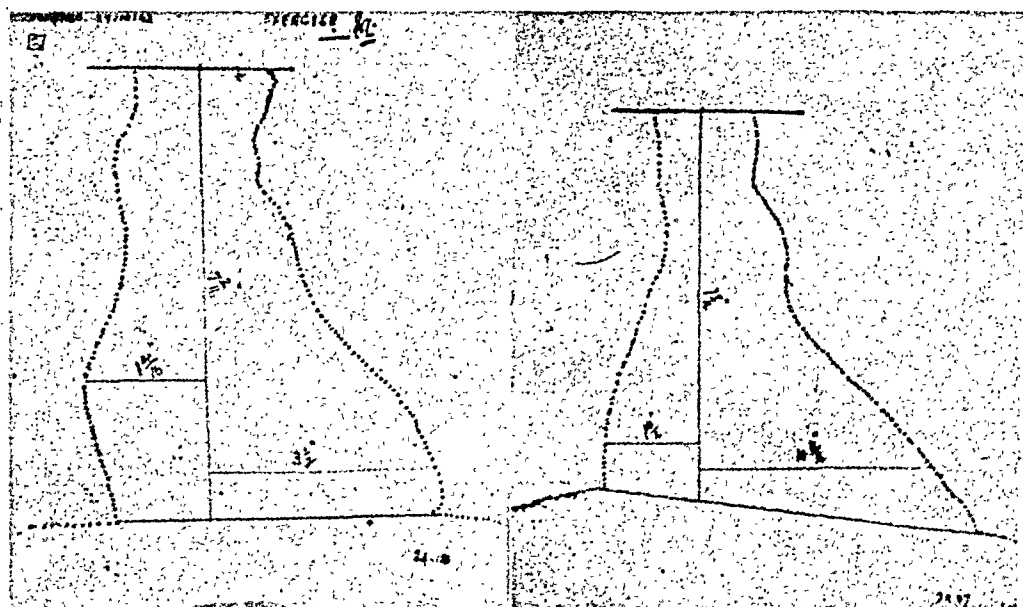


Fig. 4.

Fig. 5.

Fig. 4.—Chart of English champion, aged 35 years, middle weight. Area: 24.10 square inches.

Fig. 5.—Chart of Australian champion, aged 75 years, heavy weight. Area: 28.07 square inches. Note how pattern changes to left in the last subject.

TABLE II

AGE (YRS.)	REDUPLICATION ON LYING	REDUPLICATION ON LYING AFTER EXERCISE	REDUPLICATION STANDING AND PRONE POSITION	DURATION AFTER EXERCISE
10	0	+	0	Occasional after deep respiration
10	0	0	0	0
12	0	0	0	0
11	+	+	0	Persisted indefinitely in recumbent position
10	+	+	0	Persisted indefinitely in recumbent position
11	0	0	0	0
10	+	+	0	Persisted indefinitely in recumbent position
12	0	0	0	0
11	0	0	0	0
11	+	+	0	Persisted indefinitely in recumbent position

14.30 per cent. When this figure is compared with the percentage increase of the heart as a whole, 8.75 per cent, it seems probable that dilatation of these young hearts, after exercise, is largely, if not entirely, due to right-sided dilatation. This is in agreement with Roy and Adami's concept of the heart and its walls as those of a sphere or spheroid, and the law of strain upon the walls of a spheroid. Just as the thinnest part of a football bladder or tire is the first to bulge on increase of pressure, so the right side of the heart is the first to dilate as a result of intracardiac pressure, for the walls of the left ventricle are three times the thickness of the right ventricle. This dilatation of the right ventricle is the reason reduplication is brought on by exercise in these young hearts, and, furthermore, it is also my opinion that the association of reduplication (triple rhythm) with mitral stenosis is due to the same cause, namely dilatation of the right side of the heart. In short, reduplication of the first sound is always an indication of the dilatation of the right side of the heart whether it be in disease or after exercise.

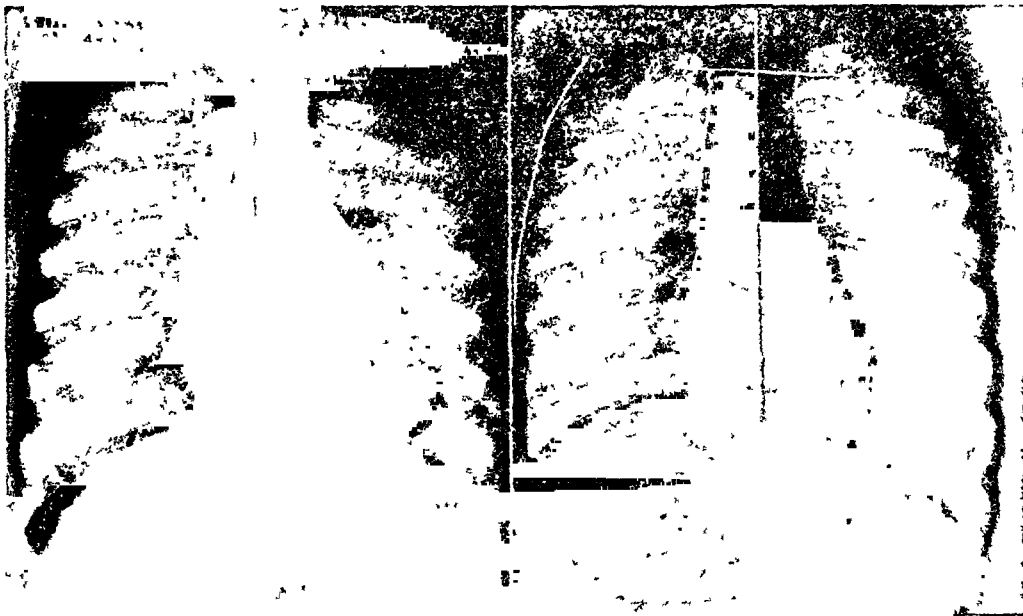


Fig. 6

Fig. 7.

Fig. 6.—Lying on left side, heart moves to the left.

Fig. 7.—Lying on right side, heart moves to the right.

The Effect of Posture on the Position of the Heart in the Thorax.—By means of a platform, subjects were x-rayed in various postures: lying on the left side, lying on the right side, suspended head downwards, and in erect, prone, and supine positions. The heart's position was found to vary with posture, e.g., when lying on the left side the heart falls towards the left, when lying on the

TABLE III. HOME GUARD

AGE (YRS.)	REDUPLICATION ON LYING	REDUPLICATION ON LYING AFTER EXERCISE	REDUPLICATION STANDING AND PRONE POSITION	DURATION AFTER EXERCISE
47	0	0	0	0
42	0	0	0	0
43	0	0	0	0
48	0	0	0	0
47	0	0	0	0
42	0	0	0	0
54	0	0	0	0
48	0	0	0	0
46	0	0	0	0
49	0	0	0	0

right side, the heart moves to the right, when standing on the head it moves downwards, dragging on the diaphragm (Figs. 6, 7, 8, and 9).

I hope later to demonstrate not only the effects of gravity on the position of the heart in the thorax and the way this varies with different postures, but, also to show that, to some extent, it rotates on its axis; this is quite feasible, since the heart is comparatively loosely suspended in the thorax and pericardium, and even the fibrous pericardium is largely interspersed with elastic fibers.

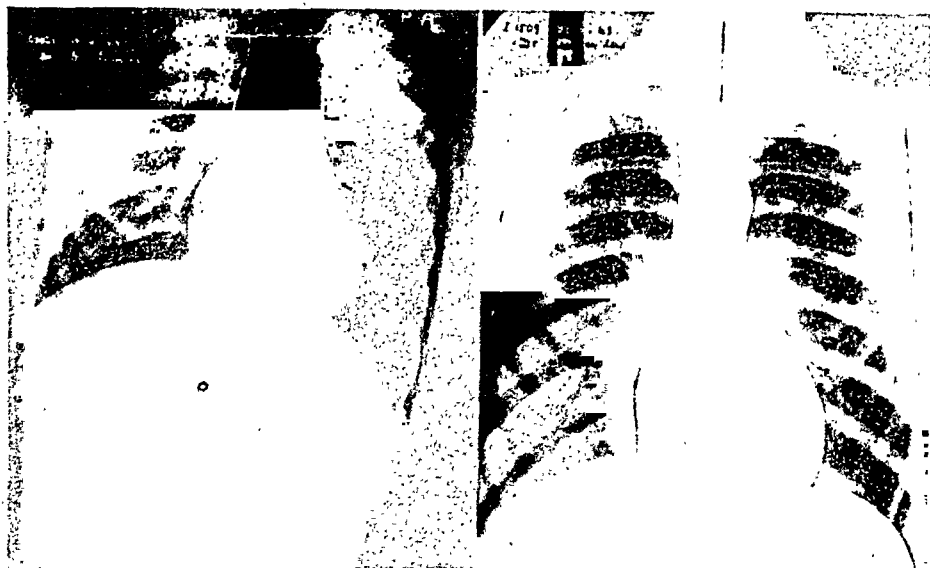


Fig. 8.

Fig. 9.

Fig. 8.—Standing on head, heart moves downward, dragging on the diaphragm.
Fig. 9.—Normal erect position.

The Audibility of Murmurs.—The audibility of a murmur, reduplication, or other cardiac sound varies with the proximity of the chest piece of the stethoscope to the source of origin of such murmur or reduplication. For example, the presystolic murmur of mitral stenosis is more audible on lying on the left side than when lying on the right, because the chest piece is nearer to the left side of the heart. The diastolic murmur of aortic regurgitation is more easily picked up in the prone position, or when the patient leans forward, because gravity causes the heart to more nearly approach the chest piece of the stethoscope. The approximation of the chest wall to the heart is the reason a systolic murmur is loudest at the end of expiration, and the presumption that, if a murmur disappears during the inspiratory phase, it must be innocent, is unsafe.

Diastolic Murmurs.—Not only have I had the opportunity of investigating diastolic murmurs in children suspended head downward, but I have also been fortunate enough to study the murmur in a gymnast suffering from double aortic disease. He could balance himself on his head for an indefinite period. My previously conceived ideas on the subject have changed. I had in the past assumed that the diastolic murmur of aortic regurgitation was influenced by gravity, but, on examining the subjects suspended head downwards, it was found that there was no difference in the audibility of the murmurs as compared with the erect position. I have come to the conclusion that the mechanism of the aortic diastolic murmur is that of backward suction; hence, it is well heard along the right border of the sternum as low as the cardiac impulse.

Diastolic murmurs are higher in pitch than systolic murmurs. Furthermore, the murmurs can be artificially produced by squeezing the bulb of a syringe; it will be found that the same rule applies—the murmur of relaxation is higher pitched than that which accompanies the squeeze. A point worthy of emphasis is that the subject with aortic disease could stand on his head for a much longer period than subjects who were used as controls; the latter soon became distressed complaining of buzzing in the ears and fullness in the head, whereas the former could remain balanced for a long period without apparent discomfort.

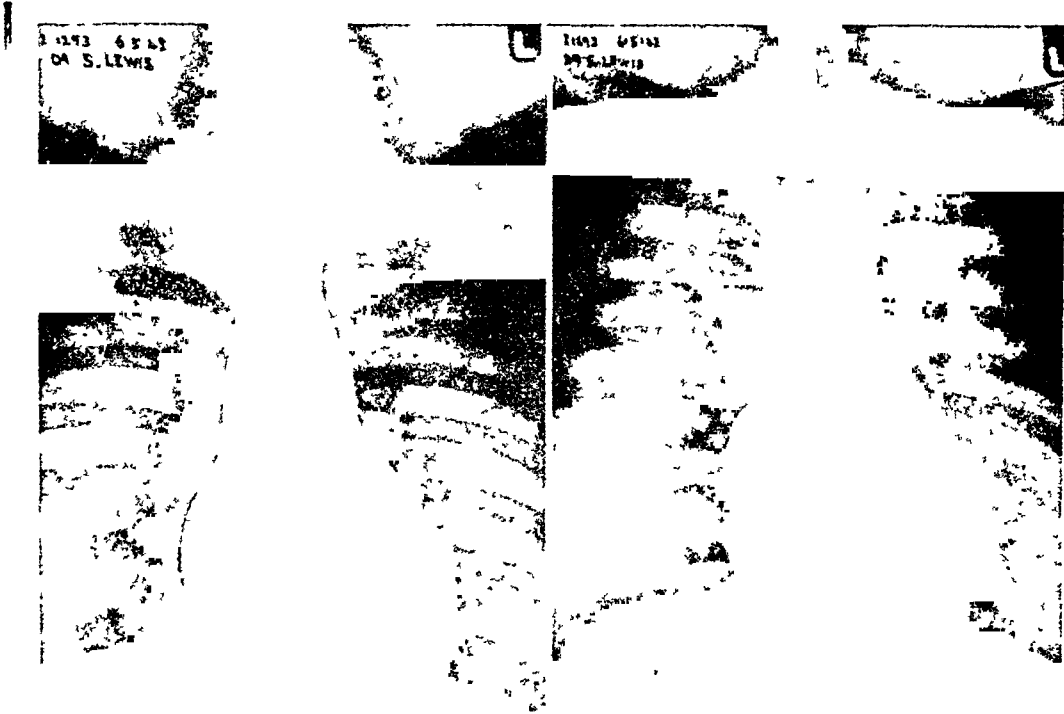


Fig. 10.

Fig. 11.

Fig. 10.—Prone. Area: 31.40 square inches.

Fig. 11.—Supine. Area: 33.80 square inches. Note how the median vertebral line shows that the heart has rotated on its axis, and how the sectional area has changed from 31.40 square inches to 33.80 square inches. The area of this particular heart in the erect position was 27.95 square inches.

Why is the reduplication more audible on lying? In the upright position the right ventricle lies between the sternum and the left ventricle, and only a very narrow strip of the left ventricle is concerned with the anterior surface of the heart. In the supine position, especially after dilatation, the effects of gravity make this relationship still more slender, and moreover this can be demonstrated by teleroentgenograms taken in the prone and supine positions, for, not only do the sectional areas of the hearts vary with change of positions, but the median vertical line shows that the heart, as a result of gravity, rotates on its axis. In the supine position the heavy left side sinks still further from the chest wall into the thorax, its place being taken by the lighter right side, which comes nearer the chest wall. This is even more marked when the right ventricle is dilated as a result of exercise in these young hearts (Figs. 10 and 11).

In other words in the supine position the right ventricle more nearly approaches the chest piece of the stethoscope than in the prone or knee-elbow position, and this explains why reduplication can be so easily picked up in the supine position as compared with the knee-elbow or prone position. This follows the law of floating spheres, i.e., when unevenly weighted, the lightest

part comes to the surface. (It is well known that changes in the electrical axis occur with change in body position.)

Heart Strain.—The influence of sudden, violent, or unduly prolonged exertion has been well described by Allbutt.¹² During the last twenty years or so it has become the fashion to assume that the healthy heart cannot be harmed by mere physical strain. I am credited with having examined more hearts of various athletes (swimmers, cyclists, weight-lifters, boxers, football players, runners, etc.) than anyone else in this country, and I have given elsewhere examples of hearts of champion athletes which have been damaged by strain and strain alone; no other cause could be found. If the heart of a champion breaks down, who is there to prove whether or not that heart was healthy at the commencement of his athletic career? At any rate, these hearts were healthy enough to enable these particular athletes to attain championship class. The only perfect heart that I can envisage is one kept beating in a glass case, free from the vitiation and vicissitudes of life.

For convenience let us divide heart strain into (a) mild heart strain, (b) moderate heart strain, and (c) severe heart strain.

TABLE IV. BOXERS' HEARTS; RATE OF PULSE BEFORE AND AFTER COMING OUT OF RING (March 22, 1943)

	PULSE BEFORE ENTERING RING	PULSE AFTER 3 ROUNDS ON REACHING DRESSING ROOM	PULSE 5 MINUTES LATER
1	84	180	120
2	92	190	160
3	84	146	120
4	120	184	160
5	92	128	88
6	100	196	166
7	104	192	140
8	92	192	128
9	96	168	80
10	104	140	120
11	88	112	110
12	68	140	90
13	88	112	160
14*	88		100
15	76	140	110
16	120	176	140

*Knocked out after second round. Incidentally, immediately after the knock out, the pupils and knee jerks were found to be unequal.

a. *Minimum Heart Strain:* As has already been shown, a mild strain of only fifty skips increases the sectional areas of the heart by 8.75 per cent. In very young hearts dilatation is even brought about by taking a few deep breaths or by mere change from the upright to the recumbent posture.

b. *Moderate Heart Strain:* The pulse rates and blood pressures of a number of service boxers taking part in three two-minute rounds were taken, and the results can be seen in Tables IV and V. There was a vast increase in both the pulse rates and the blood pressures at the end of the contests. On the other hand there was a slight decrease in the average diastolic pressure on reaching the dressing room, and indeed I have found that the diastolic pressures of champion weight-lifters are lower after the "lift" than at rest. It will be realized that there is an enormous strain on the heart even after only three two-minute rounds and that the effect on some hearts is greater than on others (Tables IV and V).

c. *Severe Heart Strain:* The following case* demonstrates the effect of severe heart strain.

*The notes of this case were kindly given to me by Dr. Ewart Evans of Birmingham.

TABLE V. BOXERS'* BLOOD PRESSURES; THE BLOOD PRESSURES BEFORE ENTERING THE RING AND IMMEDIATELY ON REACHING DRESSING ROOM AFTER FIGHTING
THREE TWO-MINUTE ROUNDS
(March 28, 1943)

	BEFORE ENTERING RING		AFTER REACHING DRESSING ROOM	
	SYSTOLIC	DIASTOLIC	SYSTOLIC	DIASTOLIC
1	145	85	180	80
2	140	82	188	70
3	145	82	180	80
4	128	80	150	60
5	140	80	150	75
6	160	60		
7	110	80	180	not taken
8	152	82	145	78
9	145	82	190	90
10	150	80	140	70
11	128	80	140	70
12	158	88	165	80
13	130	80	140	70
14	160	80	165	80
15	160	82	180	80

Before entering the ring the average systolic pressure was 143, and the average diastolic pressure was 79.

After reaching dressing room the average systolic pressure was 164, and the average diastolic pressure was 75.

It has also been found that the diastolic pressures of champion weight-lifters are lower after the "lift" than at rest.

*Average age, 22 years.

"T. W. (male) aged 27 years, solicitor, very healthy, stockily built type. No previous history of any illness. Played a very strenuous and hard fought game of 'Rugby Football.' Position—stand off half. A few minutes after the termination of the game he died.

"Autopsy, the same evening—showed dilatation of right heart, left ventricle in a state of spasm. I know that his heart was of normal size, and state, and that there were no murmurs or any signs suggesting any cardiac lesion before the game."

This case is noteworthy, and should be historic, for seldom, if ever, can there have been so little time lost in performing a post-mortem examination. Not only was dilatation of the right heart discovered, but also the left ventricle was still in a state of spasm. The post-mortem findings bear a striking resemblance to those found in thiamine deficient dogs: right auricle and ventricle dilated and the left ventricle in apparent contraction.¹⁴ It is also one more link in the chain of evidence that it is the right side which first bears the brunt after strain.

I can recall two further instances of severe heart strain which have come under my personal care; they are worthy of comment if not of emphasis. A French marathon runner, after finishing the course from Windsor to London, had complete heart block for twelve hours. I also examined Hood on the night he died at the National Sporting Club; after winning every round up to the seventeenth, he fell down unconscious, not from a blow, and never recovered.

I have elsewhere referred more fully to these and other examples of the effect of severe strain on the heart.

Training.—Cardiac endurance is measured by the ability of a heart to resist dilatation, and its ability to regain its former volume after dilatation. Gradual training brings this about by gradually increasing the tonus of the heart muscle. Roy and Adami's¹¹ law states: "the strain upon the walls of a sphere or spheroid increases with its circumference, and therefore, the resistance to contraction of the heart wall is increased whenever it becomes dilated"; i.e., the more a heart is dilated the more difficult it is for it to regain its former volume. The danger of sudden muscular effort is to produce transitory dilata-

tion of the heart and when these sudden muscular efforts become frequent, a permanent dilatation ensues, as Lord Horder,¹⁵ in a personal communication, pithily suggests, "repeated ventricular stretching must spell *harm* eventually." If the process of training be gradual and successful, the heart, instead of becoming permanently dilated, will assume a physiologic hypertrophy. It will be recalled that reduplication is uncommon as a result of exercise in the hearts of those over the age of 35 years. The heart after that age loses its dilatability and elasticity, which explains why it is difficult for a man above this age to recover second wind. The heart is like an engine, acceleration and deceleration should be gradual. It was noticeable that Lovelock and other great athletes, at the finish of a grueling race, continued for another lap, gradually decelerating; certain greyhounds, e.g., Mick the Miller, instinctively acquired the same knack. An athlete should not retire from games suddenly. Professional golfers live longer as a class than professional football players and boxers, for too many of the latter give up exercise suddenly in favor of sedentary occupations such as hotelkeeping.

Stitch in Side and Second Wind.—A certain number of recruits invariably fall out, during the course of a march, complaining of pain in the side, sometimes one side, sometimes the other. In my experience the most common location of pain is in the left hypochondrium.

I have devoted a considerable amount of time to the study of stitch and second wind, questioning numerous and various athletes, runners, rowers, boxers, swimmers, etc., and I have come to the conclusion that there are two kinds of "stitch": (1) superficial, and (2) deep.

The former has been well described by Capps,¹⁷ in 1941, and in the main I cannot cavil with his theory that it is due to anoxemia or ischemia of the diaphragmatic muscle. I would like to add that spitting has been found by generations of schoolboys to be a useful factor for giving relief. It was an added ritual that one must lift a stone, spit on it, and replace it on the same spot. This was considered to be an infallible panacea, though I have no doubt that the temporary rest and the bending over were the true reasons for the relief of the pain.

The *deep* stitch is also due to ischemia; it is dull in character, a sense of constriction or pressure, constant in position in the precordium. It is akin to cramp or angina. Jenner,¹⁶ in a letter to Heberden, in 1778, first implied the connection between ischemia and angina. I am not unmindful of the fact that the word ischemia was not then invented, yet the condition itself was well known. The explanation at which I have arrived, as a result of a wide and varied experience of all classes of athletes, is as follows: Sudden and undue effort causes the heart to contract vigorously. The metabolism of the heart, when in vigorous action, requires more frequent flushing with blood, than when it is quiescent. The forcible contraction interferes temporarily with the increased needs of the heart. It is a state of relative *ischemia* in which the coronary arteries do not admit enough blood for sudden and increased effort, thus causing pain. The pain is relieved by relaxation of the heart musculature, just as relief of cramp in the calf is brought about by flexing the big toe (which causes the calf muscles to relax).

The relaxing of the heart musculature is immediately followed by diminished resistance, and the increased intracardiac pressure acting against this diminished resistance causes dilatation of the cardiac chambers. The pain gradually disappears and the dilated heart develops a new power which enables it to complete an extraordinary task, free from pain, just when all

seems lost—*this is second wind*. I had always been dimly aware that certain athletes never have a stitch in the side, and never have second wind; this was confirmed by T. the famous varsity rowing coach. After an extensive questionnaire of athletes, I have come to the conclusion that stitch occurs only in those who have been injudiciously trained. The successfully trained athlete's heart is a racing machine from the start.

Danger Signals During Training.—The early part of training is important, for it is at the beginning that harm may be done. It is sudden strain on a sedentary heart that is harmful. The way individuals differ can be seen in the pulses of boxers before and after contests. Therefore I would suggest that the present method of submitting all the members of a unit to the same degree of training is unwise; it would be much better to subdivide them into categories, according to the way they stand training. I will now discuss a few danger signals which have appealed to me personally in my association with athletes and recruits.

As adviser to the British Weight Lifting Olympic Team, I had ample chances to study training in all its phases. In weight-lifters it was found that a constant pulse rate of 100 or over at rest, a reduplication of sound, and a sensation of throbbing or pounding in the head on stooping or lying were signals that the training for that particular athlete was too severe. I also came to the conclusion that no youth under the age of 18 years should go in for championship lifts, and moreover as a result of my examination of I. R., the champion woman weight-lifter after breaking the world's record, I formed the opinion that weight-lifting was quite unsuitable for women athletes. It is worthy of comment that this particular athlete had signs of a dilated heart, a well-marked systolic murmur, triple rhythm at rest, and poor exercise tolerance.

The pulse rate of a well-trained athlete is slower than normal, and in this connection I can recall a fight for the championship of the world between A and B. A had a pulse rate of only 56 half an hour before entering the ring, he was quite calm and relaxed, and after fighting furiously for nearly a round his pulse rate was only 110 (the fight ended unsatisfactorily towards the end of the first round). B on the other hand showed every sign of overtraining (a few months before he had been defeated after a punishing fight in America). He was fidgety and nervous during my examination; his heart was enlarged; a loud systolic murmur and reduplication could be heard at rest. His pulse rate was 98 per minute, and on reaching the dressing room his pulse rate was found to be 150 per minute. Soon afterwards, he was knocked out in his last fight before retiring for good. Yet, years afterwards, I found his pulse rate to be normal, which shows that the heart tends to recover provided the athlete slows up in time.

I fully realize that boxers are keyed up just before a fight to such an extent that one would not dare risk taking their blood pressures just before a championship fight, for fear of upsetting them. Yet, when a civilian becomes a soldier, a new factor arises, for not only is physical danger lurking near, but the specter of death may loom on the horizon. In certain people a central focus of fear is present. As a result of intensive and injudicious training such a person becomes aware of his heartbeat. The pounding of his heart at night, when alone in bed, prevents sleep; the condition may be aggravated by showers of extra systoles which are self-induced. A secret disturbance arises within the breast, at first only a tickle, gradually increasing in volume, and it only needs a shock to produce the whole psychological gamut and spate of symp-

toms known by various names—D.A.H., effort syndrome, cardiac neurosis, et cetera. Just like the bolting of a frightened horse or the running down of a piece of clockwork without its spring.

To recapitulate, the danger signals are: increased rate of pulse, increased awareness of the heart beat, reduplication at rest, sensation of throbbing in the head when lying or stooping, lassitude, and a tendency to become easily puffed. I would suggest that periodic medical inspections should be carried out in early training, so as to weed out the weak from the strong and the good from the bad, and to give the latter modified training. In that way I feel confident that breakdowns would be anticipated, and a large sum would be saved to the State in pensions. Finally, no one under the age of 18 years should be submitted to severe training. All athletic coaches are agreed on this.

SUMMARY

Reduplication after exercise is always of the first, and never of the second, sound, and reduplication of the first sound is an indication of the dilatation of the right ventricle. The right heart is the first to dilate as a result of exercise. Teleroentgenograms and accurate diagrams are given showing not only that the right side of the heart is the first to dilate as a result of exercise, but also the average increase. Teleroentgenograms have also been taken showing that the position of the heart in the thorax varies with posture, and the audibility of murmurs and reduplication in relationship to this is discussed. A detailed description of the pulse rates and blood pressures of boxers before and after contests is given. The effect of strain on the heart and its bearing on the training of the recruit is also described.

I must express my grateful thanks to the War Office and the L.C.C. for helpful cooperation; to Lord Horder for encouraging advice; to Drs. Parsons Smith and Daniel Davies for valuable help; to the x-ray staff of the County Hospital, Haverfordwest; and, in particular, to Mr. Weatherby, the radiographer.

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TRAUMATIC INJURY OF THE HEART

INCIDENCE OF ITS OCCURRENCE IN FORTY-TWO CASES OF SEVERE ACCIDENTAL BODILY INJURY

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ALTHOUGH numerous isolated cases of trauma of the heart are recorded in the literature, no investigation has, to my knowledge, been made as to the frequency of its occurrence in various accidental injuries of the body. Occasionally an author reports a series of several cases of cardiac damage due to trauma, but the causal relationship of the damage to the trauma is in many of these cases not definitely proved. Thus, Leinoff¹ reports twenty-two cases of cardiac injury resulting from accidents. Most of these, however, were first observed by the author many weeks, months, or even years, after an assumed accident, and the diagnosis of cardiac injury was based primarily on the history. Many of these were undoubtedly cases involving litigation, and the reliability of the patient's history may be questioned. Even if cardiac injury in such series of cases can be definitely proved to be due to trauma, they still do not give us any information as to the frequency of its occurrence in the usual run of accidental injuries of the body.

The first attempt to determine the incidence of cardiac trauma in bodily injuries was made by Barber.² He made electrocardiographic studies in thirty-three cases of chest injuries and found that eight of these showed abnormalities in the electrocardiogram. He selected only those cases in which the patient was less than 45 years of age, to exclude coronary disease as a possible cause for abnormal electrocardiographic changes.

Following my observations on trauma of the heart due to accidental injuries of the body in five cases previously reported,³ I carried out a cardiac study in thirty-nine cases of accidental injuries of the body in which the patients were admitted to the surgical wards of the Coney Island Hospital, and in three cases from other sources. In addition to these forty-two cases, I observed nine other cases in which there was definite evidence of cardiac involvement which, according to the history, was traceable to accidental injury. Inasmuch as these nine patients were first observed many weeks or months after the accident, they are not included in the series.

The selection of cases was based on the degree of the accident and the extent of bodily injury. The cases were not limited merely to chest injuries, as was done by Barber. The reason is that, as has been repeatedly shown by various authors, and as I have described before,⁴ trauma of the heart may occur as a result of a blow to any part of the body, provided it is of sufficient violence, and its force is transmissible to the heart. I have also included in the series individuals over 45 years of age, although coronary sclerosis might have been present in some. It is a known fact that, as I pointed out before,⁴ injury to the heart caused by a blow may occur more readily and be more severe in individuals

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of the older age groups. I made sure, however, that in all cases selected there was no history of previous heart disease. In an occasional case where there was suspicion that cardiac disease might have been present before, I made sure that the patient did not show active symptoms and signs of such disease before the accident. Furthermore, only those patients who showed active progressive electrocardiographic changes soon after the accident were included. No cases were included in which there were static abnormalities in the electrocardiogram on repeated examination after the accident.

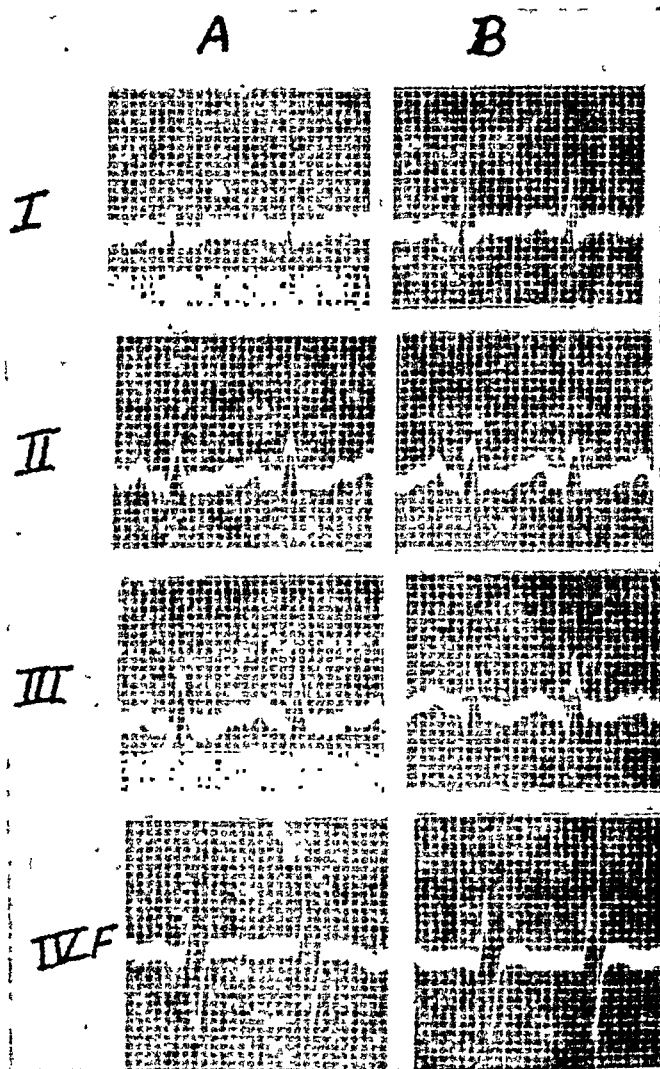


Fig. 1.—Electrocardiograms in Case 1. A, taken day of accident; B, second day.

The type of accident and the extent of general bodily injury were important guides in the selection of cases. Only those cases in which the injuries of the body were of sufficient degree to require hospitalization and in which the torsum was involved were chosen. Ambulatory patients with accidental injury were not studied.

Of the forty-two cases reported here, eleven are briefly reviewed and are accompanied by illustrations. The remaining thirty-one cases are summarized in Table I. The electrocardiographic changes of Cases 17, 18, and 19 in the table were presented in Figs. 182, 183, and 184 in the chapter on Trauma of the Heart previously alluded to.⁴

REPORT OF CASES

CASE 1.—A man, aged 41 years, with no previous history of heart disease, dived into the ocean and hit some object in the water. He fractured the right scapula, the left clavicle, the anterior part of the left second rib, and the frontal part of the skull extending to the base. He showed evidence of marked cerebral involvement. His heart was normal in size. The heart sounds were of very poor quality and a short gallop rhythm developed. He died two days after admission. The electrocardiograms in Fig. 1 were obtained on the day of the accident (*A*) and on the second day (*B*). Marked abnormalities are noted in the QRS complex and the T wave in both tracings, with progressive changes in configurations.

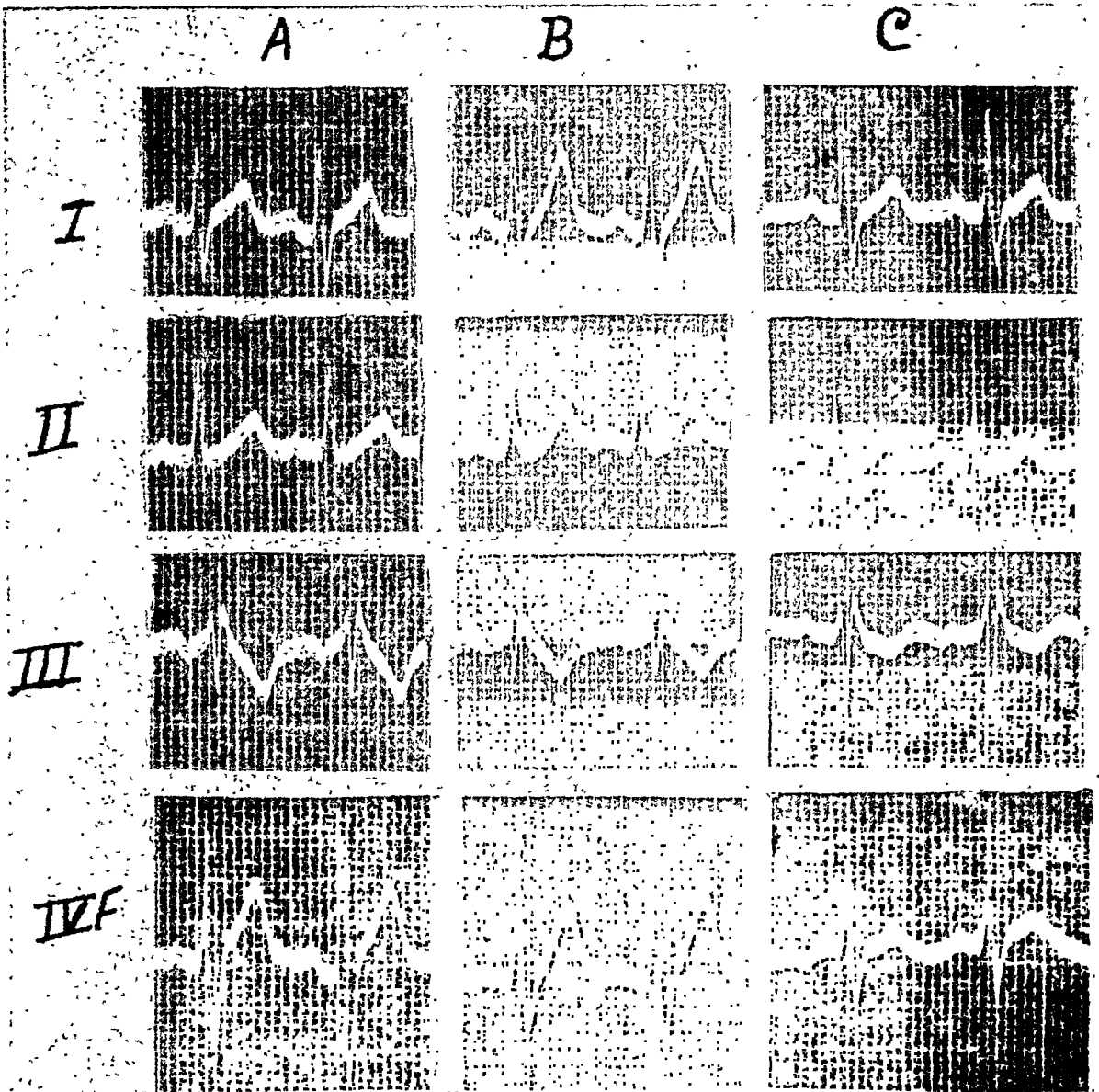


Fig. 2.—Electrocardiograms in Case 2. *A*, taken day of accident; *B*, one week later; and *C*, two weeks after *B*.

CASE 2.—An 18-year-old male with no history of any previous illness, jumped down the Marine Bridge at a height of about 30 feet. He sustained multiple contusions and abrasions of the body and fractures of the left femur and the right radius. He ultimately developed osteomyelitis of the femur and died after nine months of confinement in the hospital.

Besides the general bodily pains, due to multiple injuries, he complained of precordial discomfort. His heart sounds were muffled and split at various times. A short pericardial friction rub was heard on the tenth day of admission. A short systolic murmur developed at the apex on the seventeenth day, which later disappeared. A short presystolic gallop rhythm was present at times. At no time did he show any signs of congestive failure.

Many electrocardiograms were obtained in his case before osteomyelitis developed. Fig. 2 represents three selected tracings illustrating some of the changes in the configurations of the complexes. Record *A* was obtained on the day of the accident. There is a large S

wave in Lead I, and a tendency to left axis deviation and an abrupt QRS-T takeoff with a markedly negative T wave in Lead III. Record *B* was obtained one week later. The S wave in Lead I is of lower voltage and broadened, while the T wave is markedly exaggerated. In Lead II the R wave is of lower voltage and the R-T segment is rounded. In Lead III the QRS complex is of lower voltage and the T wave is less negative. In Lead IVF, the S wave is of lower voltage and broadened, and the S-T segment is very abrupt. Record *C* was obtained two weeks after *B*. At this time there is a greater degree of left axis deviation with diminished voltage of the T wave in Leads I, II, and IVF. The T wave in Lead III is diphasic.

CASE 3.—A man, aged 40 years, was struck by an automobile and sustained fractures of the left radius and ulna, the right radius, the right tibia and fibula, the left fourth rib in the midaxillary line, and the acromium process of the left scapula. He had general bodily contusions and abrasions. In addition to generalized pains, he complained of precordial pain the first few days. His heart was not enlarged, but the first sound was diminished in intensity from time to time during the first two weeks. He recovered completely from all his injuries after three months confinement in the hospital.

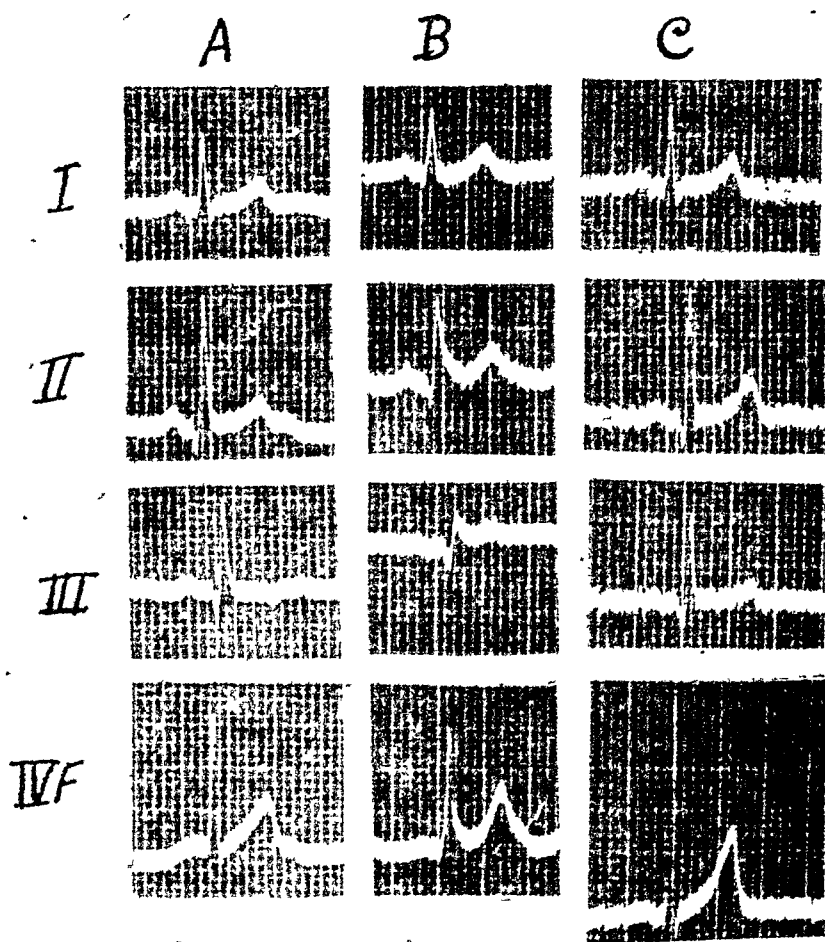


Fig. 3.—Electrocardiograms in Case 3. *A*, *B*, and *C*, taken two, fifteen, and eighteen days, respectively, after the accident.

Many electrocardiograms were obtained in his case, three of which are shown in Fig. 3. Record *A* was obtained two days after the accident. It is within normal limits. There is a large U wave present, shown particularly in Lead II. Record *B* was obtained fifteen days after the accident. The voltage of the R wave in all leads, especially in the third, is much lower, the R-T segment is rounded in all leads and elevated in Leads II, III, and IVF, and the T wave is of higher voltage in all leads, being positive instead of negative in Lead III. Record *C* was obtained eighteen days after the accident. The tracing is similar to that of Record *A* except that the T wave is of higher voltage in Leads I and II, positive in Lead III, and both the QRS complex and T wave are of much higher voltage in Lead IVF. The U wave is absent in all leads. Sub-sequent tracings obtained on him showed no further changes.

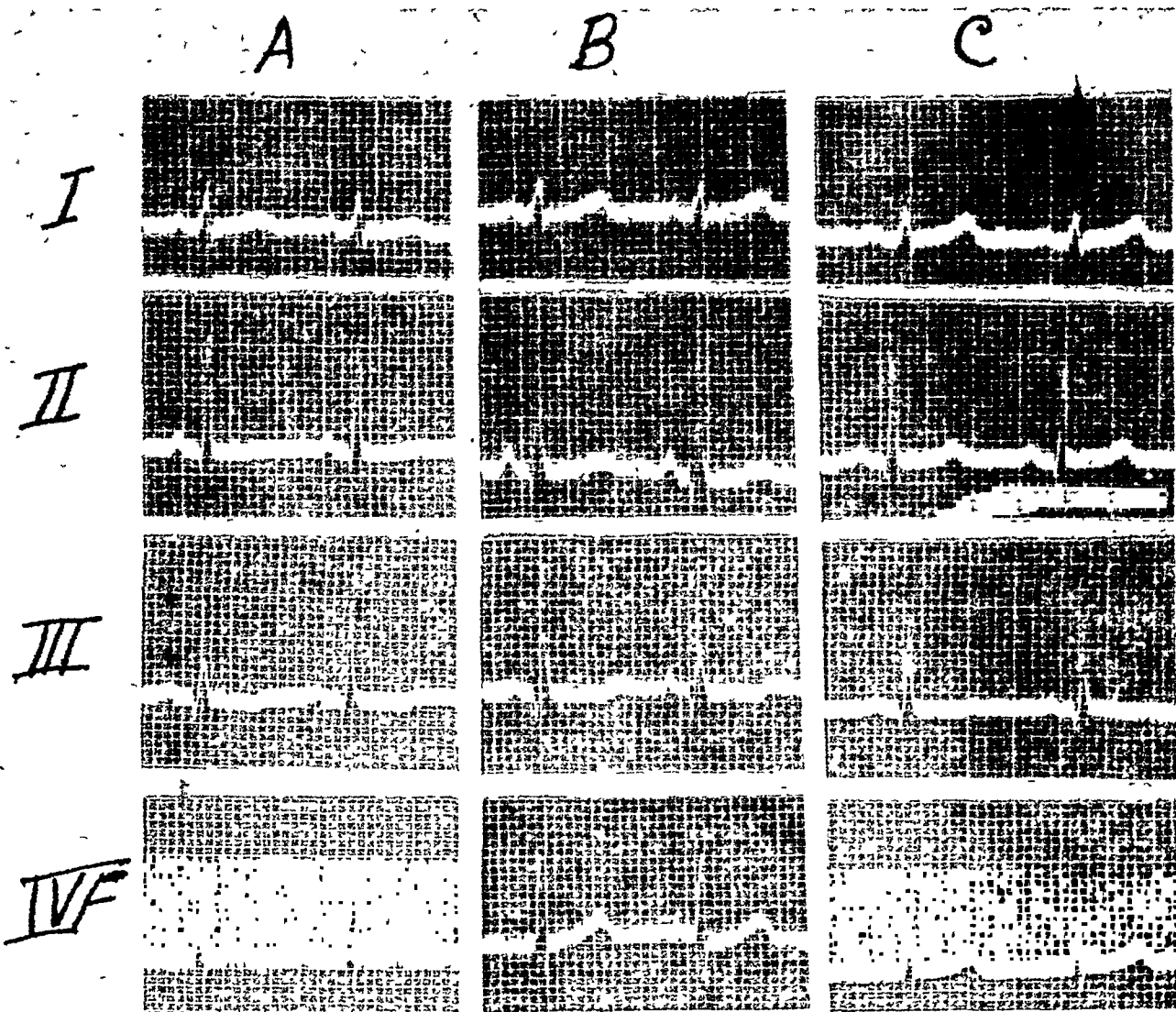


Fig. 4.—Electrocardiograms in Case 4. A, B, and C, taken several hours, two days, and twenty days, respectively, after the accident.

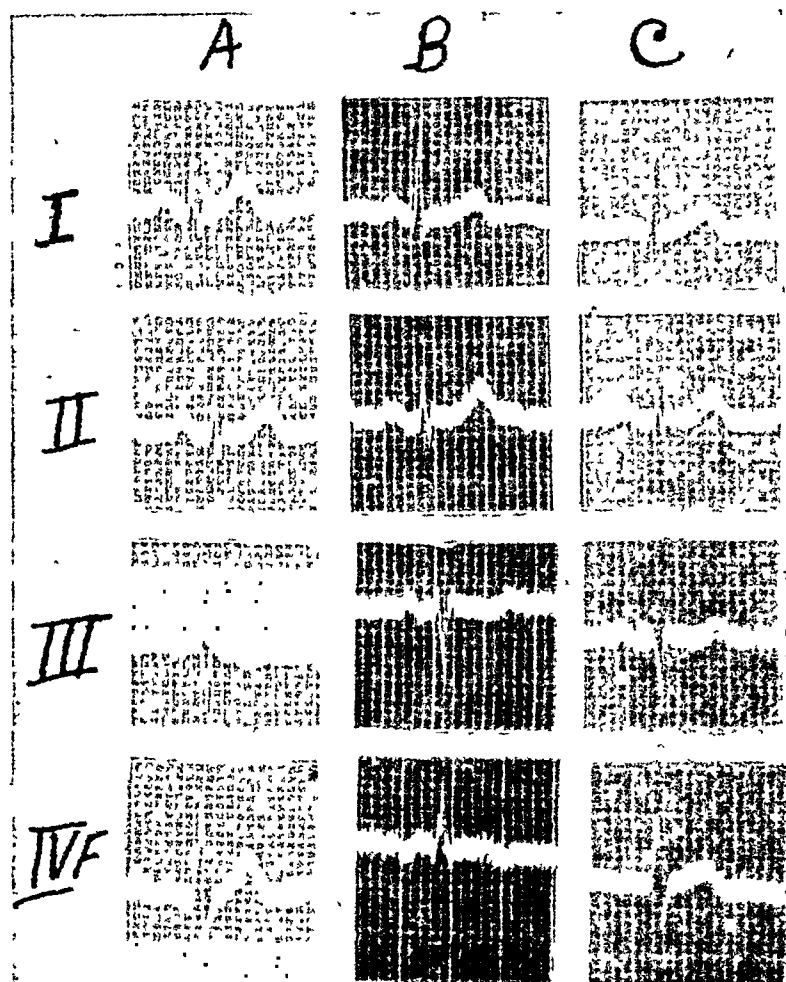
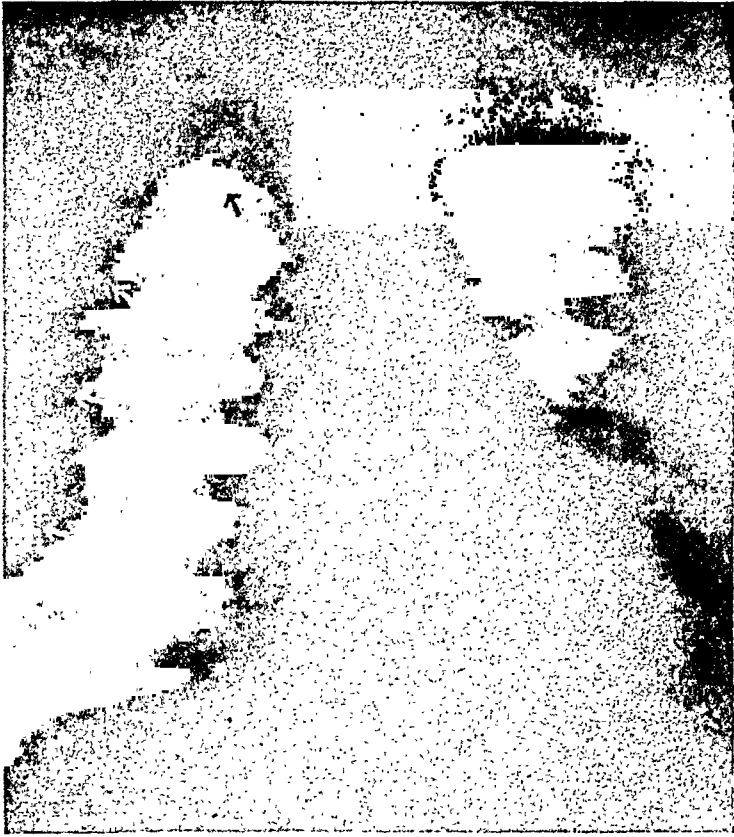


Fig. 5.—Electrocardiograms in Case 5. A, B, and C, taken one, four, and six days, respectively, after the accident.

CASE 4.—A man, aged 44 years, who was always well, was struck by a car and sustained fractures of the right tibia and fibula, multiple fractures of the pelvis, fractures of the right fifth and sixth ribs in the midaxillary line and contusions and abrasions of the body. He completely recovered after thirty-two days' stay in the hospital. There were no symptoms or abnormal physical signs of heart involvement.



A.



B.

Fig. 6.—Teleroentgenograms in Case 6. A and B, taken one and nine days, respectively, after the accident. Arrows point to the edge of the compressed lung by the pneumothorax.

The electrocardiogram (Fig. 4, *A*) was obtained several hours after the accident. The T wave is of low voltage in Lead I, almost isoelectric in Lead II, negative in Lead III, and of very low voltage, diphasic, in Lead IVF. Fig. 4, *B*, was obtained two days after the accident. The QRS complex is of higher voltage in Leads II, III, and IVF. The T wave is of higher voltage in Leads I, II, and IVF. Fig. 4, *C*, was obtained twenty days after the accident. Its appearance is the same as in *B* except that the QRS complex in Leads II, III, and IVF is now of the same voltage as in the corresponding leads in *A*. The relatively low voltage R wave in Lead I in this case is due to a longitudinally shaped heart which he presented.

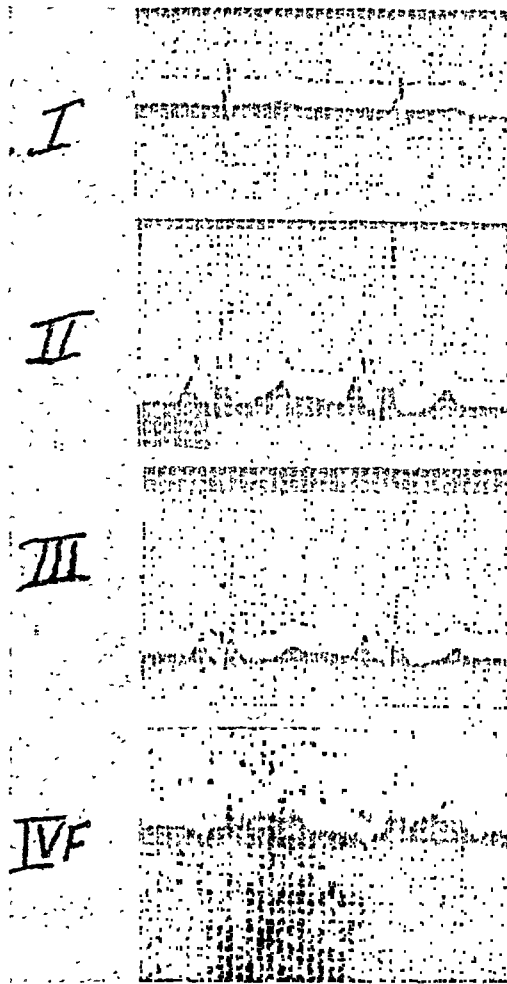


Fig. 7.—Electrocardiogram in Case 6.

CASE 5.—A woman, aged 49 years, was struck by a car and sustained contusions and abrasions of the body and lacerations of the face. There were no fractures of bones. She complained of general bodily pains and marked precordial oppression. There was tenderness over the left upper anterior chest. The size of the heart was normal, and the rhythm was regular, but the first sound was very short and of valvular quality. A faint systolic murmur was heard over the apex during the first two days. The heart sounds returned to normal after several days.

Fig. 5, *A*, depicts her electrocardiogram one day after the accident. It shows merely left axis deviation. Fig. 5, *B*, was obtained four days after the accident. The T wave in Lead I is of lower voltage. In Lead IVF, the P wave is negative, the R wave is of low voltage and markedly notched, the S wave is almost absent, the S-T segment is coved, and the T is negative. Fig. 5, *C*, was obtained six days after the accident. The R wave in Lead I is of lower voltage, the QRS complex in Lead II is multiphasic and of much lower voltage, and the appearance of the ventricular complexes differs from these of *A* and *B*.

CASE 6.—A man, aged 36 years was struck by an automobile and was brought to the hospital in a stuporous condition. He showed marked contusions and abrasions of the body. An x-ray film of his chest one day later (Fig. 6, *A*) shows right pneumothorax with collapse of about one-third of the right lung. The heart and mediastinum are deviated to the left. There are no fractures of any of the bones of the chest. In an x-ray film taken eight days

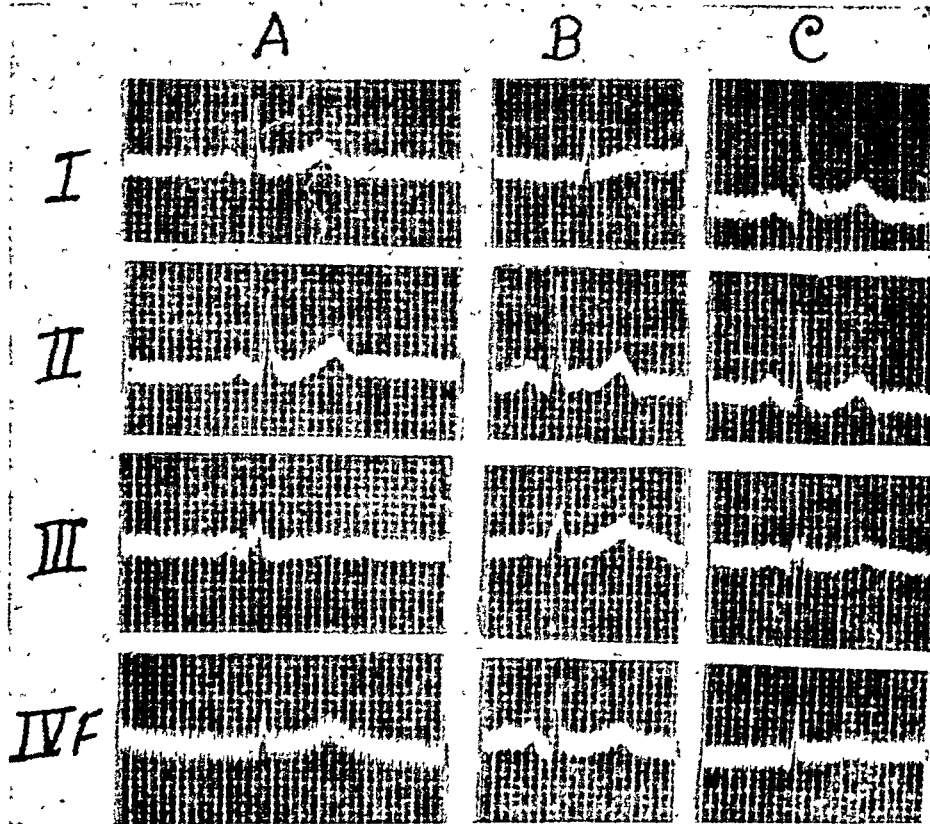


Fig. 8.—Electrocardiograms in Case 7. A, B, and C, taken one, four, and twenty days, respectively, after the accident.

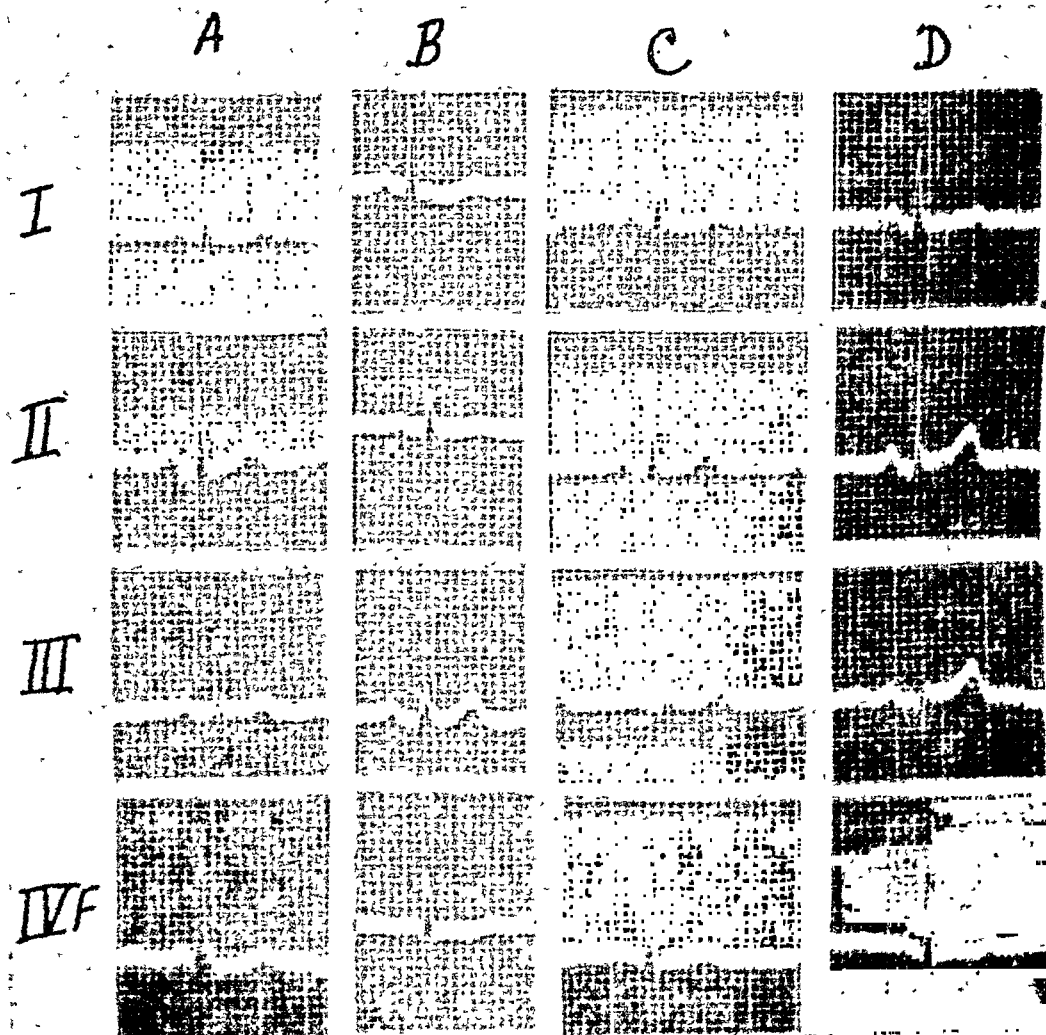


Fig. 9.—Electrocardiograms in Case 8. A, taken soon after the accident; B, C, and D, two, four, and six days later, respectively.

later (Fig. 6, *B*), the pneumothorax is slightly less marked. The heart sounds were of poor quality, and a short systolic murmur was heard over the aortic area.

Electrocardiograms, obtained on the second, third, fourth, fifth, and ninth day after the accident were alike, without progressive alterations; one is shown in Fig. 7. The low voltage ventricular complexes in Lead I are probably due to shift of the heart to the left, although the possibility that it may be due to structural damage of the heart is to be considered.

CASE 7.—A girl, aged 19 years, was thrown off the running board of a fast moving automobile. She sustained multiple contusions and lacerations of the body and a fracture of the skull. She made a complete recovery after a stay in the hospital of about ten weeks. Her heart showed no detectable abnormalities the first eight days. On the ninth day, she developed a loud systolic murmur between the third and fourth intercostal spaces, close to the sternum, and the heart rate increased from 72 per minute, in the recumbent posture, to 125, when she attempted to sit up. She had no subjective complaints referable to the heart. The murmur disappeared entirely after ten days.

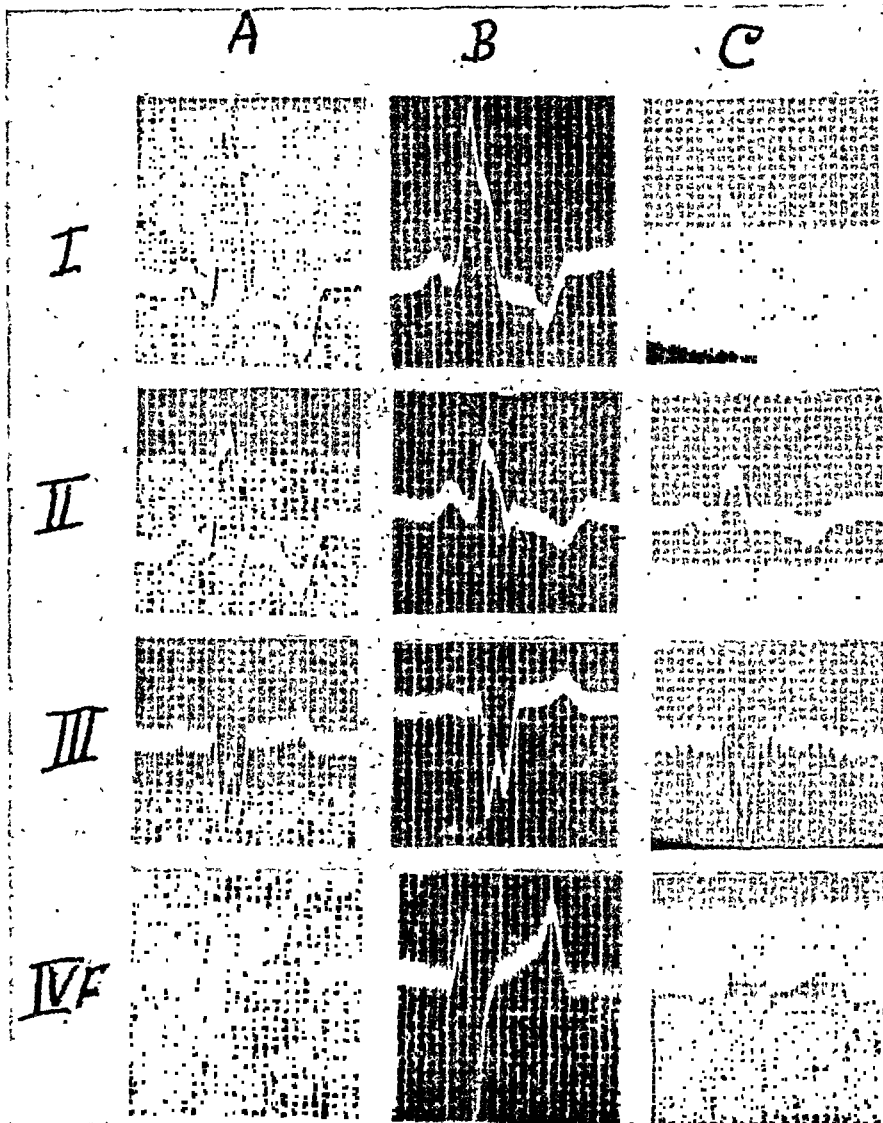


Fig. 10.—Electrocardiograms in Case 9. *A*, *B*, and *C*, taken two, four, and eleven days, respectively, after the accident.

In Fig. 8, *A*, *B*, and *C*, are three electrocardiograms obtained one, four, and twenty days, respectively, after the accident. In *A* the QRS complex in Lead IVF is of low voltage. In *B* the QRS and T waves in Lead I are of lower voltage than in *A*, while those of the other leads are of higher voltage than before. In *C* the findings are practically the same as in *A*.

CASE 8.—A woman, aged 62 years, was hit by an automobile and was thrown to the ground. She sustained a fracture of the left femur and marked contusions of the body especially the left side of the chest. No ribs were fractured. Her heart was slightly enlarged, the first sound was somewhat diminished in intensity, and the second sound at the aortic area

was accentuated. There was a rough systolic murmur over the aortic area, transmitted over a fairly large area, which was undoubtedly present before the accident and indicated pathologic changes of the aorta. Her blood pressure measured 200/100. She had moderate peripheral arteriosclerosis and the x-ray examination showed calcification of the abdominal portion of the aorta. She undoubtedly had considerable coronary sclerosis with myocardial damage before the accident.

Fig. 9, *A*, is a tracing obtained from her soon after the accident. The T wave in Leads I and IVF is of low voltage, and there is some depression of the R-T segment in the latter lead. Fig. 9, *B*, was obtained two days later. The voltage of the QRS complex in Lead I is higher, while in the other leads it is lower, than in *A*. There is some depression of the R-T segment in Lead I. The T wave is of lower voltage in Lead II, higher in Lead III, and lower in Lead IVF. Fig. 9, *C*, obtained four days after the accident, shows further changes, especially in Lead IVF, which now approaches a more or less normal appearance. The general appearance of the three leads is approximately the same as the corresponding leads in 9, *A*. Fig. 9, *D*, obtained six days after the accident, is about the same as 9, *C*, except for a somewhat higher voltage T wave in Leads II and III and the presence of a fairly large Q wave in Lead III.

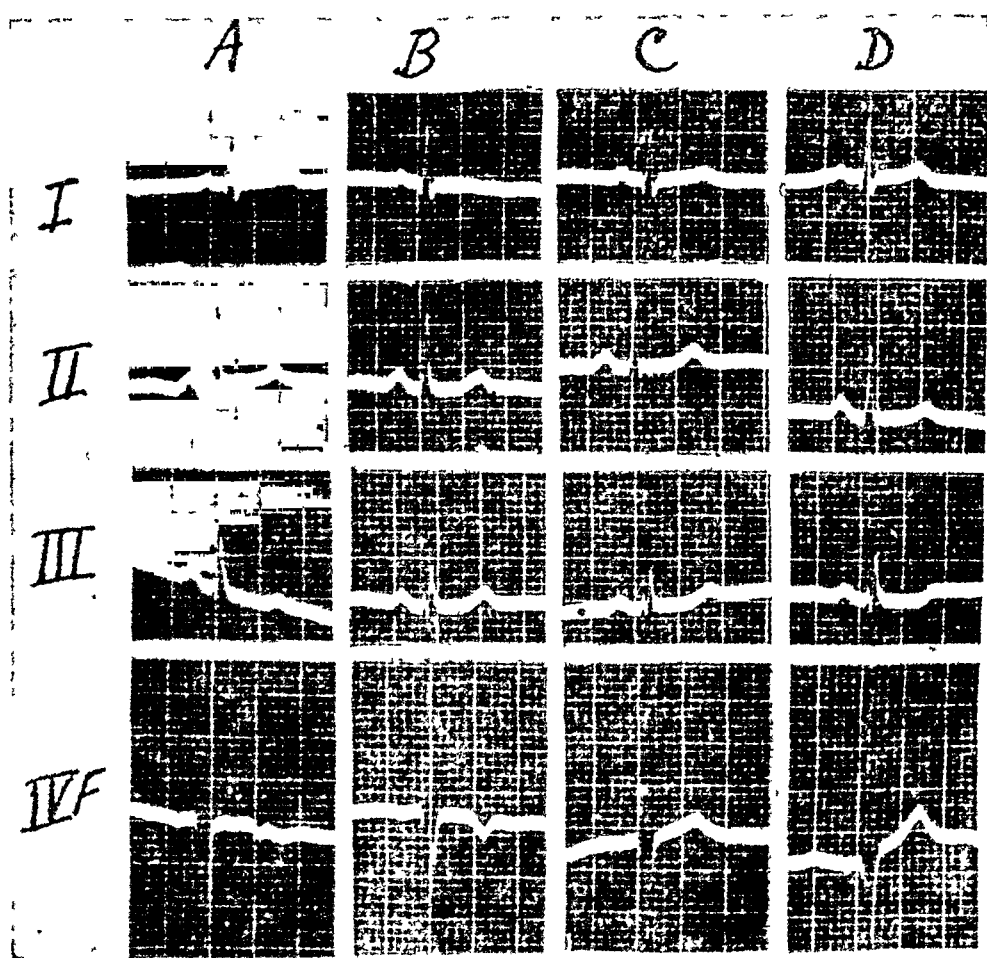


Fig. 11.—Electrocardiograms in Case 10. *A*, *B*, *C*, and *D*, taken twelve, twenty, twenty-eight, and thirty-six days, respectively, after the accident.

CASE 9.—A man, aged 67 years, fell on the ground and sustained a fracture of the left humerus, the left third, fourth, and fifth ribs, and contusions of the chest. He complained of pain in the injured areas, but there were no symptoms referable to the heart. He recovered completely. His heart was enlarged, and the sounds were of the type often heard in cases of bundle branch block. There was moderate congestion at the bases of the lungs. He had marked generalized arteriosclerosis.

An electrocardiogram (Fig. 10, *A*) was obtained two days after the accident. It shows left bundle branch block. Fig. 10, *B*, four days after the accident, still shows left bundle branch block, but some changes are noted in the configuration of the complexes, especially in

Lead II. Fig. 10, *C*, eleven days after the accident, shows further changes in the configuration of the ventricular complexes; left bundle branch block is still present. The bundle branch block probably existed before the accident, but the changes in the appearance of the complexes from time to time assume significance in indicating acute alterations in intraventricular conduction.

CASE 10.—A male, laborer, aged 51 years was excavating a ditch and was buried up to his neck by a heavy bank of ground which caved in. He sustained fractures of the pelvis and the free costal cartilages of the left ninth, tenth, and eleventh ribs. A day later, he began to experience retrosternal pain, radiating to the left shoulder, with choking sensation and a feeling of suffocation. This continued with greater or less severity for many weeks. His heart was not enlarged, and the sounds were accentuated. No murmurs were audible. An electrocardiogram, twelve days after the accident (Fig. 11, *A*), shows a low voltage T wave in all standard leads and a peculiar triphasic T wave in Lead IVF. Twenty days after the accident (Fig. 11, *B*), the T wave is isoelectric in Lead I, more positive in Leads II and III, and markedly negative in Lead IVF. Twenty-eight days after the accident (Fig. 11, *C*), the T wave in Leads I and IVF is positive but of low voltage, while in Leads II and III it remains the same. Thirty-six days after the accident (Fig. 11, *D*), the T wave is of higher voltage in Leads I and IVF.

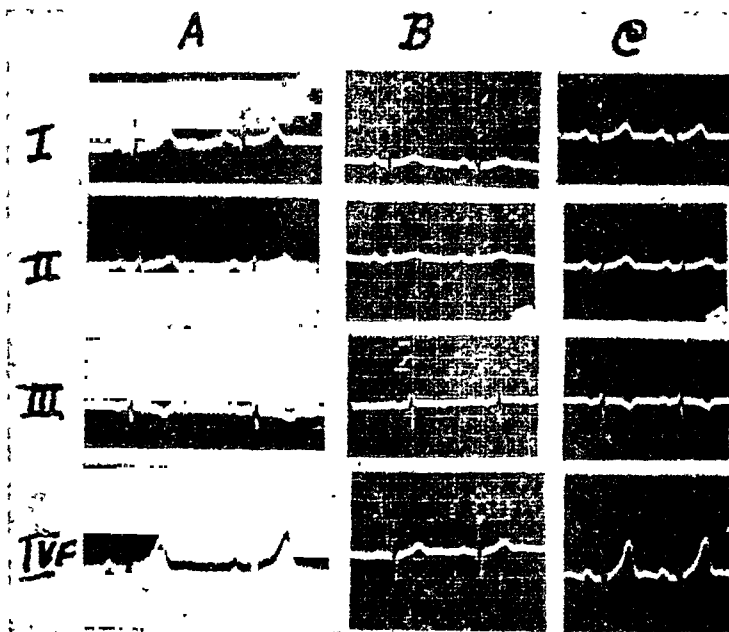


Fig. 12.—Electrocardiograms in Case 11. *A*, taken one and one-half years before the accident; *B* and *C*, six days and seven weeks, respectively, after the accident.

CASE 11.—A male physician, aged 46 years, while driving his car, collided head-on with another car and was thrown against the steering wheel. He sustained fractures of the second to the sixth right ribs at the costochondral junction with displacement. The angle of Louis became exaggerated, but there was no demonstrable fractures of the sternum. There was little shock but some pain was present in the sternal region on breathing or on moving around. He was admitted to a hospital where he stayed ten days. At the end of this time he felt well enough to return to his practice. While in the hospital, the heart sounds, as recorded by his attending physician, were normal, and repeated examinations failed to reveal any murmurs. An electrocardiogram he had obtained about one and one-half years before the accident (Fig. 12, *A*) shows a tendency toward left axis deviation. One obtained six days after the accident (Fig. 12, *B*) shows a definitely lower voltage T wave in all leads. Another tracing obtained about seven weeks after the accident (Fig. 12, *C*) is the same as the one before the accident.

About three weeks after the accident a loud systolic murmur was heard throughout the precordium by several physicians who examined him. I saw him for the first time about seven months after the accident when he presented a harsh systolic murmur occupying almost the entire systolic period with its maximum intensity at the third left intercostal space, close to the sternum, transmitted throughout the precordium, as far as the left anterior axillary line in the fifth space, and upwards as far as the right clavicle. The heart rate was 96 per minute and the rhythm was regular. The heart sounds were of good quality.

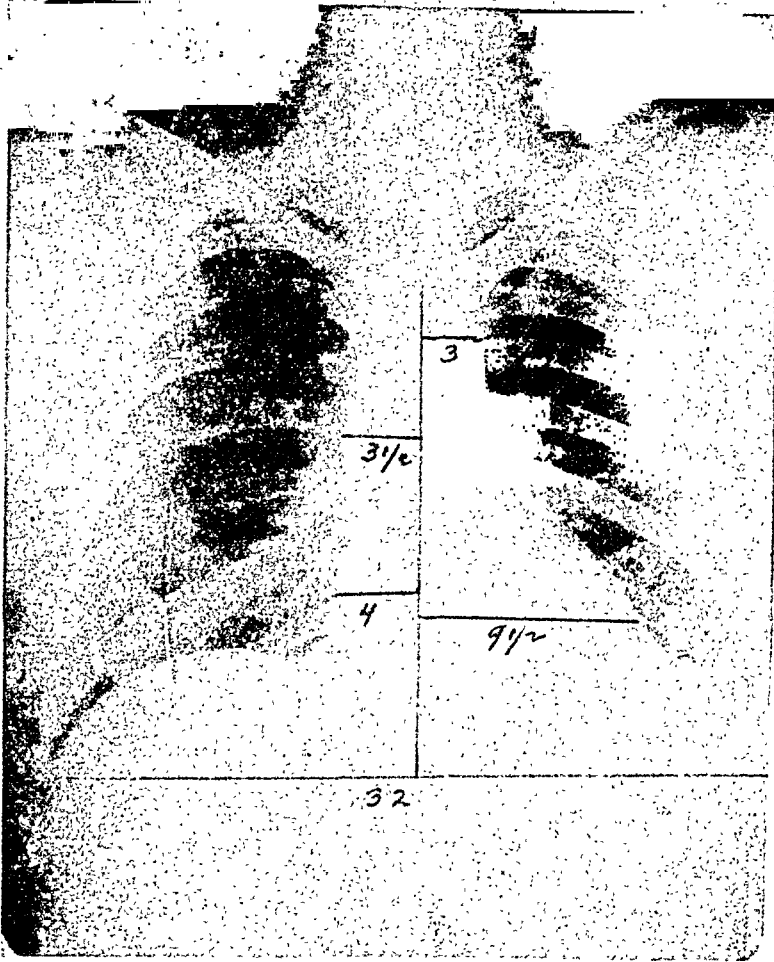


Fig. 13A.—Teleroentgenogram in Case 11, taken thirteen days after the accident. The figures represent the diameter in centimeters.

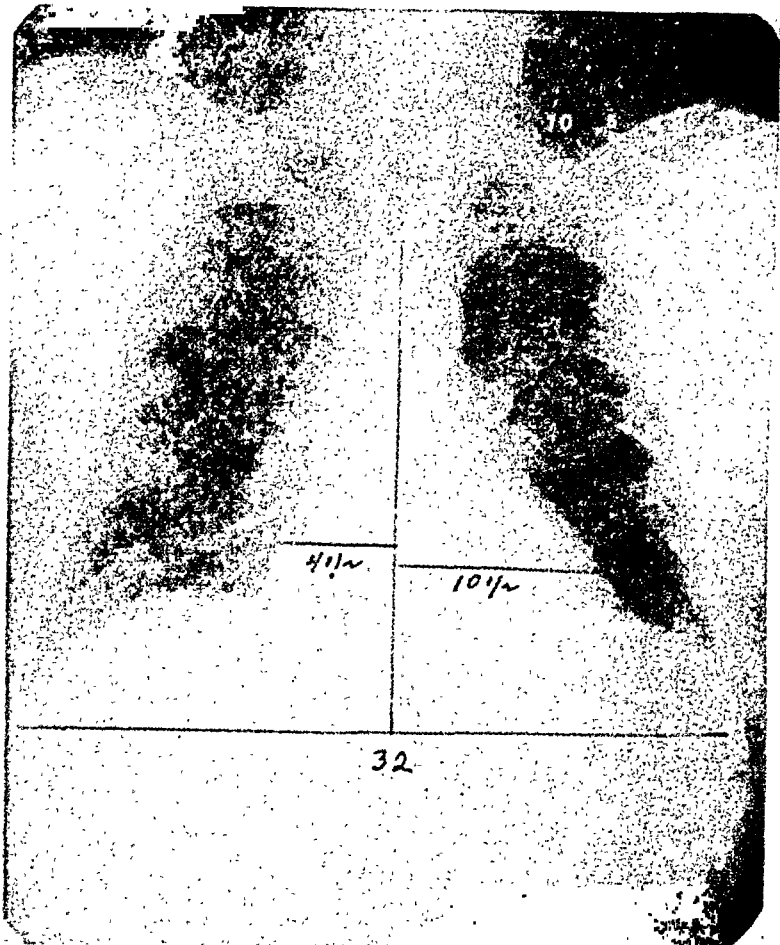


Fig. 13B.—Teleroentgenogram in Case 11, taken seven months after the accident. The figures

Inasmuch as the patient lives a great distance away from New York, I had no opportunity to observe him further. Frequent communications received from him, now nearly three years after the accident, indicate that he is able to continue his practice. He lives a comparatively strenuous life without any undue discomfort. His heart is moderately enlarged to compensate for an interventricular septal defect which he evidently developed as a result of the accident. The enlargement is shown in Figs. 13A, 13B, and 13C, obtained about thirteen days, seven months, and one year, respectively, after the accident.

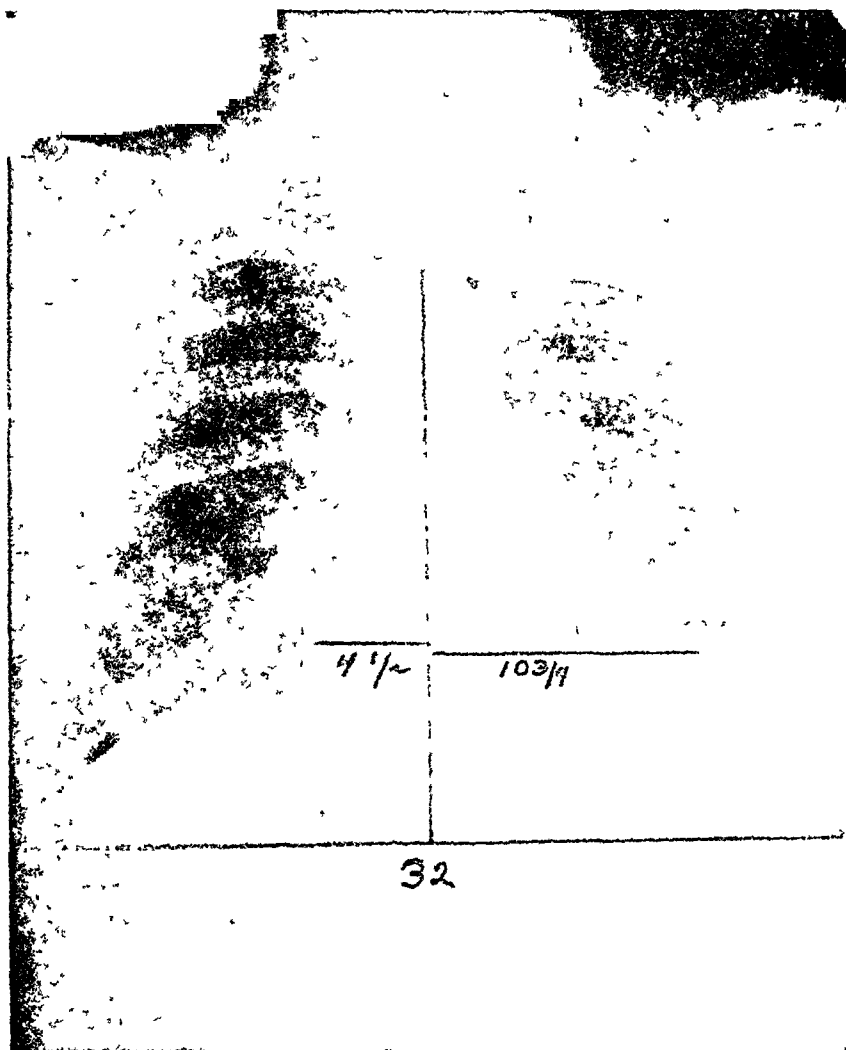


Fig. 13C.—Teleroentgenogram in Case 11, taken one year after the accident. The figures represent the diameter in centimeters.

DISCUSSION

It will be noted from the review of the forty-two cases reported here that cardiac damage occurs rather frequently in association with the general run of accidental bodily injuries, if the blow is of sufficient severity. In the forty-two patients, thirty-two, or 76.2 per cent, had demonstrable, cardiac injury, either clinically or electrocardiographically or both. Of these thirty-two patients, twenty-two had injuries of the chest wall, in addition to other bodily injuries, and, in ten others, the chest wall was not injured. Of those with chest-wall injuries, fifteen had fractures of one or more ribs and seven others had merely contusions and abrasions. If the degree of the blow to the chest can be measured by the presence or absence of fractures of ribs, we may assume that the blow to the chest in the seven patients without fractures was not marked, and the main force that injured the heart was transmitted from other parts of the body. In other words, in seventeen cases out of thirty-two with demonstrable cardiac injury, the transmitted force producing such injury came either entirely or mainly from other parts of the body.

- TABLE I

CASE SEX AGE (YR.)	NATURE OF ACCIDENT	BODILY INJURIES	ABNORMALITIES OF HEART		
			DAYS AFTER ACCIDENT	SYMPTOMS AND ABNORMAL PHYSICAL FINDINGS	ELECTROCARDIOGRAMS
12 Male 53	Struck by automobile	Fracture of 8th, 9th, 10th, 11th, and 12th left ribs in anterior axillary line	1 2 4, 7, 9, and 12	Dyspnea, precordial pain. Normal find- ings Same Same	Normal Slightly higher voltage R ₁ Same as on second day
13 Male 28	Struck by bus	Basal fracture of skull, cerebral hem- orrhage	2 3 4, 5, and 7	Nothing abnormal Nothing abnormal Nothing abnormal	Left axis deviation Less left axis deviation, large QRS ₁ and T ₁ Same as 2 days after accident
14 Male 16	Fell off truck which was running at high speed	Fractured skull, brain injury	Same 4 7	None None None	Normal Bradycardia, T ₁ much higher voltage Normal; same as on first day
15 Male 59	Struck by automobile	Comminuted fracture of tibia and fibula, followed by osteo- myelitis, septic temperature, ampu- tation and death 2½ months later	Same 2 6	None Poor first sound, sys- tolic murmur at apex and pericar- dial friction rub at apex Heart sounds better; no rub	Tendency, left axis deviation T wave lower voltage in all leads Same as 2 days after accident
16 Female 57	Struck by automobile	Fractured pelvis, con- cussion of brain	19, 20, 26, 31, and 38	Enlarged heart, mark- edly diminished first sound, fre- quent premature contractions, sys- tolic at base trans- mitted to apex	Low voltage T ₁ , tendency to left axis deviation, ventricular premature contraction, later T ₁ isoelectric and T ₂ and T ₃ low voltage, T ₄ negative
17 Female 18	Thrown off car at high veloc- ity in amuse- ment place	Severe body injuries, fracture right 11th and 12th ribs, rup- ture right kidney, liver injury, frac- ture right radius	1 5 7 and 13	Short gallop apex, systolic murmur over pulmonic area Same None	T ₁ isoelectric, T ₂ and T ₃ slightly diphasic, T ₄ negative T ₁ slightly positive Normal
18 Male 50	Fell from sec- ond-story window	Fractured skull and multiple fractures left 3rd, 4th, and 5th ribs and left clavicle, shock	Same 2 12	Muffled, soft first sound, shock Precordial pain, muffled sounds Sounds better quality	T ₁ low voltage, T ₄ diphasic Very low voltage T ₁ , all leads R-T ₁ and R-T ₂ elevated, T waves normal in all leads
19 Female 40	Struck by au- tomobile	Multiple fractures of pelvis, body con- tusions	1 4 6 18	None Epigastric and retro- sternal pain, 2 days Same None	Normal T ₂ and T ₄ negative, changes in voltage of QRS T ₁ and T ₂ lower, T ₃ iso- electric, T ₄ Slightly positive. Nor- mal
20 Female 70	Thrown to ground by bicycle	Fractured right radius and ulna	1 8 14	None None None	Normal Higher voltage in Leads I, II, and IVF Still higher voltage in Leads I, II, and III, lower IVF

TABLE I—CONT'D

CASE SEX AGE (YR.)	NATURE OF ACCIDENT	BODILY INJURIES	ABNORMALITIES OF HEART		
			DAYS AFTER ACCIDENT	SYMPTOMS AND ABNORMAL PHYSICAL FINDINGS	ELECTROCARDIOGRAMS
21 Male 58	Struck by automobile	Fracture of left tibia and fibula and 5th to 7th left ribs	1 10	None None	Normal Lower voltage QRS with rounding of R-T seg- ment, all leads
			20	None	Normal, same as one day after accident
22 Male 8½	Fell from a height of 12 feet, striking wooden fence	Laceration and large hematoma of liver at surgical opera- tion	8 10	None None	None T ₁ lower voltage
23 Male 28	Struck by automobile	Contusions and abra- sions whole body, no fractures	2	Poor quality first sound	Negative T waves in Leads II, III, and IVF
24 Female 37	Fell down a flight of stairs	Fracture left femur, contusion of left chest and body	4 weeks	Precordial pain, dys- pnea, weak sounds	Low voltage T wave, all leads, with slight de- pression of R-T seg- ment
25 Male 13	Fell down while skating	Fracture left arm and contusions of chest	1 2	None None	Normal No change
26 Female 54	Hit by a man and fell to ground	Transverse complete intra-articular frac- ture right radius, multiple fracture of pelvis	2 3, 7, 11, 14, and 21	None, blood pressure 160/80 None	Normal No change
27 Male 3½	Fell 18 feet from win- dow	Cerebrospinal injuries	8 and 10	None	Normal
28 Female 22	Struck by car, thrown to ground	Contusions of body, laceration of scalp	4 6, 13, and 17	None None	Rounding R-T ₂ and R-T ₃ Normal, no change
29 Female 14	Struck by automobile	Concussion of brain	2 and 3	None	Normal
30 Male 65	Struck by foot- ball player, fell	Fracture of greater trochanter	3 5, 6, 9, and 16	None None	Left axis deviation Lesser left axis deviation but no changes
31 Male 48	Fell down one flight of stairs	Contusions and abra- sions of chest, sprain right ankle, cerebral concussion	2 3, 4, 6, 7, and 10	Precordial pain, diminished first sound Diminished pain, sounds normal	Normal Normal, slight change in T ₂ from time to time
32 Female 47	Fell to ground	Fracture of right fibula	2 and 5	None	Tendency to left axis deviation, no changes
33 Male 57	Struck by au- tomobile, fell on but- tocks	Fracture shaft femur and fibula. Died 10 days later from pul- monary emboliza- tion	2, 4, 6, and 9	None	Left axis deviation
34 Male 41	Struck by automobile	Contusions and abra- sions of body, frac- ture 9th and 12th right ribs, shock	Same 4 and 7	Chest pain, cough cyanosis. Greatly diminished first sound Sounds better. Gen- erally better	Left axis deviation Left axis deviation, no change
35 Male 76	Struck by automobile	Contusions of left chest	Same 1, 3, and 9	Chest pain. Split first sound Chest pain. Split first sound	Normal No change

TABLE I—CONT'D

CASE SEX AGE (YR.)	NATURE OF ACCIDENT	BODILY INJURIES	ABNORMALITIES OF HEART		
			DAYS AFTER ACCIDENT	SYMPTOMS AND ABNORMAL PHYSICAL FINDINGS	ELECTROCARDIOGRAMS
36 Male 12	Struck by automobile	Fracture left tibia and fibula and right tibia	2	None	Normal
			8	None	Normal but lower voltage complexes
			11	None	Normal
37 Male 30	Struck by automobile	Injury left chest; fracture neck of 3rd left rib	1 and 6	Precordial and left chest pain. Dimin- ished first sound	Normal
38 Male 40	Auto collision, thrown against steer- ing wheel	Fracture right 3rd rib, secondary pleurisy	Same	Sounds muffled	Tendency left axis devia- tion
			2, 4, and 6	Sounds gradually im- proved	Lower voltage QRS
39 Female 44	Struck by automobile	Compound fracture left tibia and right fibula, contusions of body	2	Precordial pain. Ac- centuated first sound, short gallop	Tendency left axis devia- tion
			6, 9, and 21	Return to normal sounds	Gradual increase of left axis deviation
40 Male 57	Struck by automobile	Fracture of femur, severe contusions and lacerations of chest and face	2	None	Normal
			16	None	Same
41 Male 25	Fell on ground, striking chest	Contusions of chest, no fractures	1 to 3	Precordial pain faint- ing	None obtained
			4	Severe attack of re- trosternal pain several hours	T ₁ and T ₂ negative
42 Male 52	Driving bus, collided with streetcar. Thrown against steer- ing wheel	Contusion of chest	Same	Collapse, cold clammy perspiration, ex- cruciating pre- cordial pain	None obtained
			3	Continuous pain.	Left axis deviation very
			15	Faint heart sounds Signs of left ven- tricular failure	low voltage QRS T ₂ and T ₃ negative. Left axis deviation, T ₁ negative, T ₂ slightly positive, T ₃ negative

It is interesting to find, as illustrated in Case 6, that injury to the lung may also occur without any damage to the chest wall. That is, under certain circumstances, a transmitted force from distant parts of the body may also produce other intrathoracic injury than that of the heart.

How trauma of the heart is produced by a blow to distant parts of the body cannot be easily explained. To my knowledge, no experimental studies of this problem have, as yet, been carried out. In the studies of the relation of heart injury to trauma carried out by Schlomka,⁵ Kulbs and Straus,⁶ Bright and Beck,⁷ Kissane, Fidler, and Koons,⁸ Moritz and Atkins,⁹ and Randles, Gorham, and Dresbach,¹⁰ injury of the heart was produced by direct blows to the chest or by blows to the exposed heart. No study has been made of the possible production of cardiac injury by severe blows applied to other parts of the body.

There are, however, many reports of isolated clinical cases of cardiac injury and rupture following an accidental blow to distant parts of the body. The cases of Howat,¹¹ Saphir,¹² Kampmann,¹³ Kienle,¹⁴ and Smith and McKeown¹⁵

are only a few of the many found in the literature. It is undoubtedly the suddenness of the blow applied to the body and transmitted to the heart by the severe vibrations set up which results in the injury. It is possible that, in some cases, the damage of the heart is not produced directly by the transmitted force on the heart muscle but by coronary spasm induced by the blow, resulting in myocardial ischemia. This theory was postulated by Schlomka⁵ in his experimental work and may also apply to the human being. The subject has been described in my previous communication.⁴ The factor of shock, with its emptying effect on the coronary system, also may play a part.

The cardiac injury in our series was usually manifested soon after the accident. In some cases there was a delay of one or more days before symptoms and signs or electrocardiographic evidence developed. In many of these cases the clinical and electrocardiographic manifestations were very mild in degree and short-lived so that they could easily have been missed if frequent examinations had not been made.

The subjective manifestations were precordial discomfort in one case; precordial pain in nine cases; precordial pain together with dyspnea in two; retrosternal and epigastric pain in one; retrosternal pain radiating to the left shoulder, together with choking sensation in one; and chest pain, cyanosis, and cough in another. Seventeen patients had no subjective complaints. In general, the subjective complaints suggestive of cardiac injury were mild compared with complaints referred to other bodily injuries.

The objective manifestations consisted of changes in the character of the heart sounds and the presence of a gallop rhythm, a pericardial friction rub, murmurs, and premature contractions.

The changes in the character of the heart sounds were usually short-lived. In eleven cases, the first or first and second sounds were diminished in intensity. In three cases the sounds were muffled. In one the first sound was split, in another it was of valvular quality, and in two the sounds were accentuated. In three cases a gallop rhythm developed, lasting a few days, and in a fourth case a gallop rhythm was associated with marked diminution in the intensity of the first sound. A pericardial friction rub occurred in two cases and was fleeting.

The murmurs heard were all systolic in time. In three cases it was heard at the apex with a comparatively small area of transmission. In three cases it was heard at the aortic area, but there was good reason to feel that in two (Cases 8 and 16) it was present before the accident and was due to pre-existing, atherosclerosis of the aorta. In one case the murmur was heard at the left sternal border, between the third and fourth intercostal spaces, and in one over the pulmonic area. In Case 11, the maximum intensity of the murmur was in the third left intercostal space with wide transmission, typical of the so-called Roger's murmur which goes with interventricular septal defect. Premature contractions occurred in one case.

The electrocardiographic changes were not specific and varied with different cases. The characteristic findings were frequent alterations in the configuration of the various deflections from day to day, or in the course of days in each case, as described before.⁴ The changes consisted of occasional alterations in the P wave; changes in the direction of the electrical axis from time to time; and alterations in QRS complex, in the RS-T segment, and in the T wave.

The changes in the QRS complex consisted of variations in the heights of its various components from time to time, the development of slurring and notching

in occasional cases, and the appearance or disappearance of some of the waves of the complex.

The changes in the RS-T segment often consisted of rounding, elevation, and upward concavity in one or more leads seen in pericardial involvement. In occasional cases there was some coving as seen in myocardial infarction. In most cases the changes were nonspecific.

The T-wave abnormalities consisted of diminution in its height and change in its direction from positive to isoelectric and negative in various leads from time to time.

The pathologic changes that occur in the heart in trauma are probably the same as in the experimental animal, reported by the observers previously alluded to⁵⁻¹⁰ and were fully described before.⁴

The outcome of traumatic injury to the heart in this group of cases was generally good. Complete recovery apparently occurred in nearly all cases. This was undoubtedly due to prolonged rest in bed which the other bodily injuries called for. In Case 1, in which the patient died, the cause of death was at least partly due to the cardiac injury, which was very marked. In Case 2, the patient died after many months from osteomyelitis, not primarily from his cardiac condition. In Case 11, the damage is permanent as judged by the persistence of signs, now, three years after the accident.

In a previous communication³ I reported one case of traumatic injury of the heart which was observed for more than two years. At the end of this time the patient showed complete clinical recovery, but Lead IVF in the electrocardiogram still showed abnormalities. In another case the patient showed evidence of severe myocardial and pericardial disease with calcification and auricular flutter, three and one-half years after an accident. One year later, he died in heart failure. A third patient still shows evidence of extensive organized posterior wall infarction with the anginal syndrome, now over four years after an accident.

Some years ago,¹⁶ I reported an unusual case of left-sided displacement of the heart which I considered at that time to be probably of congenital origin. The patient, however, gave a history that, as a child, he fell from a window three stories high, and was bedridden about three months. In the light of subsequent experiences, I must agree with Bramwell and King,¹⁷ who think that the abnormality in this case was probably caused by traumatic injury rather than due to a congenital defect. King reported two more somewhat similar cases, one his own and another by Howard, in both of which trauma, resulting in massive pleuropulmonary pericardial adhesions, was the cause of retraction of the heart to the left.

Although the number of cases presented in this paper is small, the frequency of occurrence of cardiac injury in this series is very significant. Such injury would certainly have been overlooked if no special investigation were made. The complaints of the patient referable to the heart were comparatively trivial and could have easily been missed by the surgically minded doctor.

The problem of trauma of the heart in bodily injuries certainly calls for further unbiased investigation, not colored by preconceived ideas. The study should include careful clinical, electrocardiographic, and other laboratory follow-up, of all severely injured patients, from the day of injury through recovery. Those that show some permanent defect of the heart should be observed for years to ascertain the ultimate outcome. The statement by Stroud,¹⁸ "I

still feel cardiac injury is unusual following anterior chest trauma," frequently expressed also by other cardiologists, is certainly based on nothing more than belief.

SUMMARY

A study was made of the incidence of trauma of the heart in forty-two cases of rather serious accidental injuries to the body. In thirty-two, or 76.2 per cent, there was demonstrable evidence of some cardiac damage, clinical, electrocardiographic, or both. In some cases the damage occurred even if the blow did not affect the chest, provided it was of sufficient severity to result in marked bodily injury. In most cases the damage appeared to be very mild and short-lived. In some it was severe.

In many cases there were either no subjective manifestations referable to the heart or the manifestations were trivial. Precordial pain or discomfort and slight dyspnea were the main complaints. The objective manifestations consisted of abnormalities in the heart sounds, the presence of a gallop rhythm, a pericardial friction rub, and systolic murmurs, in various areas. The findings were short-lived and occurred in comparatively few cases.

The electrocardiographic manifestations consisted of changes in the voltage and appearance of the QRS complex from time to time and some shift in the electrical axis; elevation, rounding with upward concavity, and occasional coving of the R-T segment; and frequent changes in the T wave from positive to isoelectric and negative and back to positive. In the majority of cases the electrocardiographic changes were nonspecific. In occasional cases, they were characteristic of pericardial involvement, or of localization of the damage to other specific areas of the heart.

Complete recovery took place in nearly all cases in this series. Only one patient showed permanent damage and in another case the cardiac injury was at least partly responsible for death.

The observations tend to indicate that trauma of the heart is a rather frequent occurrence in serious bodily injuries and call for future unbiased investigation of this subject.

I am indebted to Drs. D. A. McAteer, J. E. Hammett, J. E. Miles, and G. Webb, for the privilege accorded me of carrying out the observations presented in this paper on patients from their surgical services.

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STUDIES CONCERNING THE ETIOLOGY AND PATHOGENESIS OF NEUROCIRCULATORY ASTHENIA

III. THE CARDIOVASCULAR MANIFESTATIONS OF NEUROCIRCULATORY ASTHENIA

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INTRODUCTION

IN PRECEDING articles,^{1, 2} the nature and pathogenesis of hyperthermia, giddiness, and syncope, found in the syndrome of neurocirculatory asthenia (NCA), were discussed. As a result of these studies, attention was directed toward the hypothalamus as a possible factor in the pathogenesis of the somatic phase of this illness. In the present communication, the results of clinical, physiologic and pharmacologic studies of the cardiovascular manifestations of neurocirculatory asthenia are reported.

In the past, there has been considerable disagreement concerning the exact status of the cardiovascular system in the patient with NCA. Some investigators³⁻⁶ have not been able to detect any significant, or persistent, defect in the hemodynamics of these patients, but others⁷⁻¹⁰ have reported abnormalities in either the size of the heart, in its function, or in its conduction system. It is worthy of emphasis, too, that whereas most internists^{4, 8, 11} have consistently stressed the psychic factors in this disease, they have not succeeded in integrating the latter in any exact, physiologic manner with the actual emergence of cardiovascular symptoms and signs in the same patient. Likewise, the psychiatrists have not succeeded in elucidating the pathogenesis of cardiovascular manifestations in patients suffering from an obvious anxiety neurosis. There exists, then, a physiologic or neurologic void between the psychic and cardiovascular phases of neurocirculatory asthenia which has not been probed sufficiently by either the internist or by the psychiatrist. Until this void is explored, however, it will be impossible to understand those processes set loose in a person subject to anxiety, which express themselves in trembling, perspiration, flushing, dyspnea, palpitation, and precordial pain.

In an attempt to investigate the physiologic connection between the admitted emotional turmoil of the patient with NCA and his cardiovascular symptoms and signs, a study was made of fifty young soldier patients suffering from this syndrome. In this investigation, the hemodynamics of the patient with NCA

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were not studied solely as the functional expressions of isolated tissues containing and propelling blood, but rather as reactions of the entire cardiovascular system, a system intimately connected to the remainder of the body and controlled by nerve and by chemical reactions. For it is clear that any study of the heart and the organs associated with it *demands* such correlation. Otherwise, there is danger of grave inaccuracy, despite the use of the most precise devices designed to measure isolated hemodynamic functions.

A. PHYSICAL EXAMINATION OF THE HEART

Several workers^{12, 13} have reported a small incidence of actual valvular heart disease in their series of patients with NCA. I was unable, however, to detect a single case of either congenital or infectious heart disease in my series. Inconstant, systolic, apical murmurs were heard in ten patients (20 per cent), but they lacked the identifying characteristics suggestive of damaged valves. Four patients (8 per cent) exhibited sharp, forceful heart beats against relatively thin chest walls.

B. THE SIZE OF THE HEART (ROENTGENOGRAPHIC DETERMINATION)

Although Master⁷ has reported that the heart of the patient with NCA may be abnormally small, other investigators^{3, 5} have found no particular abnormality in the size of this organ. Teleroentgenograms of the hearts of twenty patients with NCA and of fifteen normal young adults were obtained, measured, and compared. It was found that the average cardiothoracic ratio of the patients with NCA was 0.407 (range: 0.330 to 0.450) and that of the controls was 0.402 (range: 0.335 to 0.440). Thus, no abnormality in the size of the heart was found in the average patient with NCA in the present series. Furthermore, no abnormalities were found in the size or contour of the separate chambers of the heart.

C. ELECTROCARDIOGRAPHIC STUDIES

Both Master⁷ and Merritt¹⁰ have reported abnormalities of either the QRS complex or of the T wave in electrocardiograms obtained from patients with NCA. I was unable, however, to detect any significant, fixed abnormality in electrocardiograms of thirty patients with this syndrome. Nor was I able to confirm Master's observation that there is frequently a right axis deviation in the electrocardiogram of such patients.

In sharp contrast to the observations of other investigators,^{4, 12, 14} I found that eleven of my patients (22 per cent) exhibited some form of transient arrhythmia during their hospital stay. Four had bouts of paroxysmal auricular tachycardia, five exhibited ventricular extrasystoles, one had transient episodes of auricular flutter, and one exhibited a wandering auricular pacemaker. The high incidence of arrhythmia in my series of patients might have been due to the fact that, besides obtaining routine electrocardiograms on admission, I also obtained additional ones when the patients informed me that they were experiencing palpitation. This last procedure was undertaken because it allowed the observation of the patient at the exact instant he was aware of heart dysfunction and enabled me to check in an objective fashion what he felt subjectively.

Two of the four patients with NCA who suffered from attacks of auricular paroxysmal tachycardia as frequently as five times a day were observed on several occasions before, and during, a bout of paroxysmal tachycardia. Invariably it was found that the onset of the arrhythmia was preceded by marked accentuation of the hand tremor, elevation of the oral temperature to hyperthermic

levels (99.2° to 100° F.), perspiration of the axillary and palmar skin, facial pallor, and a feeling of nervousness or tension. These symptoms and signs continued as the tachycardia began and persisted for a short while after the tachycardia had been interrupted by pressure over the carotid sinuses. It was found, too, that, when these same patients were given quinidine, their attacks of arrhythmia ceased, but they continued to experience and show, at intervals, the symptoms and signs previously described. This separation of the prodromal syndrome and the tachycardia itself, following the administration of quinidine, strongly suggested that the tachycardia observed was not the cause, but the result, of the peculiar nervous discharge which was seen to precede and accompany it.

D. OBSERVATIONS CONCERNING EXERCISE TESTS IN THE EVALUATION OF CARDIOVASCULAR EFFICIENCY

There has been some disagreement about the value of exercise tests in the evaluation of the patient with NCA. Several observers^{4, 13} report that such a patient may show abnormalities in pulse and respiratory rates following such tests whereas other investigators^{3, 6, 12, 15} have insisted that the usual exercise tests are of no value in detecting, or assessing, cardiac derangement in this type of patient. In connection with cardiac efficiency, the observations of Starr⁹ are of interest in that he found some patients with NCA who exhibited hypofunction of the heart and others who showed hyperfunction.

TABLE I. THE RESPIRATORY RATE, PULSE RATE, AND BLOOD PRESSURE OF PATIENTS WITH NCA AND NORMAL ADULTS BEFORE AND AFTER A STANDARD EXERCISE TEST

CASE	BEFORE TEST			IMMEDIATELY AFTER TEST			TWO MINUTES AFTER TEST		
	RESP.	PULSE	B.P.	RESP.	PULSE	B.P.	RESP.	PULSE	B.P.
<i>Patients With NCA</i>									
1	20	80	135/72	28	140	170/80	28	104	120/80
2	20	96	130/95	36	150	155/90	20	108	135/95
3	20	100	115/75	48	130	150/70	34	100	135/75
4	18	118	110/80	28	156	140/75	20	138	115/80
5	20	96	145/100	36	140	210/90	24	126	170/90
6	20	72	120/75	18	84	130/75	20	74	120/65
7	20	84	130/75	34	120	135/70	26	96	130/70
8	18	112	120/80	36	144	130/70	22	118	120/80
9	24	96	135/78	32	144	160/60	32	114	155/70
10	18	88	120/70	48	168	135/70	24	114	120/80
11	20	64	135/80	36	120	170/70	42	68	145/80
12	36	88	110/70	42	168	135/65	36	98	110/70
13	24	104	110/75	36	144	130/70	30	96	110/70
14	20	80	115/80	36	160	135/80	24	120	115/80
15	20	90	120/85	24	156	145/75	24	114	135/80
16	18	68	115/70	30	120	130/70	18	60	120/70
17	20	76	135/80	24	132	180/70	21	90	135/60
18	18	78	135/80	24	120	150/70	18	80	140/75
19	20	84	130/90	22	132	140/90	20	84	130/90
20	25	104	120/80	36	192	165/70	32	120	130/80
21	24	88	115/60	38	168	155/70	30	108	125/70
22	18	100	115/75	30	192	125/65	20	102	120/70
Average	21	89	123/79	33	144	148/73	26	101	128/80
<i>Normal Adults</i>									
1A	16	76	110/75	32	120	130/65	18	72	110/70
2A	20	88	120/80	24	132	155/65	24	90	130/75
3A	14	84	95/55	20	144	120/50	14	80	100/60
4A	24	80	110/80	30	120	140/90	24	78	135/75
5A	18	84	120/80	18	144	165/55	18	76	135/75
6A	20	88	125/70	24	120	145/80	20	72	125/75
7A	18	84	125/85	24	132	150/70	24	94	125/65
8A	23	72	125/70	24	120	145/60	20	76	120/70
9A	20	78	125/65	25	180	165/55	21	81	124/65
Average	20	82	117/73	24	135	146/65	20	80	124/71

In our own efforts to determine the cardiac efficiency of the patient with NCA, we first employed a standard exercise test in which the patient jumped up and down (both feet together) one hundred times in sixty seconds. Measurements of the blood pressure, pulse, and respiratory rates were obtained before, immediately after, and again two minutes after, the performance of the test. Twenty-two patients with NCA and nine normal adults were studied. As Table I indicates, the resting values of the two groups were approximately the same. Other than excessive tachypnea in the patients with NCA, the values were also similar immediately after the performance of the test. When, however, the measurements taken two minutes after exercise were compared, it was found that the average pulse and respiratory rates of the patients with NCA were abnormally high.

On superficial analysis, the results above might seem to indicate a relative cardiac inefficiency in neurocirculatory asthenia. However, as mentioned before, it would be a mistake to assume, on the evidence of a persisting tachypnea and tachycardia alone, that these patients possessed an inadequate cardiovascular system. Other factors might have been responsible for the persistent tachycardia and the tachypnea. For example, it was found that quite frequently the patient with NCA, at the very beginning of the test, exhibited a tachypnea which was out of all proportion to the amount of work done up to that time. Accordingly, before the heart could be ascribed as the primarily deranged organ and the cause of the persisting tachypnea and tachycardia, the following observations had to be performed: (1) the effect of voluntary tachypnea on the pulse rate, (2) assessment of cardiac efficiency by other methods during the period of tachypnea and tachycardia after the standard exercise, and (3) the determination of the pulse and respiratory rate in an exercise test in which the possibility of anxiety on the part of the patient was eliminated.

1. *The Effect of Voluntary Tachypnea on the Pulse Rate.*—Seven patients with NCA and seven normal young adults were instructed to breathe deeply thirty times in forty seconds after their resting pulse had been taken. It was found that the patients with NCA showed an average increase of 30 beats per minute and the control group exhibited an average increase of five beats per minute after the hyperventilation had been completed. Four of the seven patients with NCA also exhibited a pounding heart and complained of palpitation. One also complained of precordial pain. These results indicated that tachypnea itself could induce an abnormal response in the cardiovascular functions of the patient with NCA. It suggested, too, that the high pulse rate observed in such a patient after the completion of the standard exercise test could have been caused by the tachypnea—a tachypnea which occurred so near to the onset of the test that it could not have been due to cardiac insufficiency.

2. *Assessment of Cardiac Efficiency During Standard Exercise Test by Measurements of the Vital Capacity, Venous Pressure, and Circulation Time.*—The vital capacity of seven patients with NCA was taken before and immediately after the performance of the standard exercise test. As Table II shows, the average vital capacity of the patient with NCA before and after exercise was 2.31 and 2.27 liters per square meter of body surface, respectively. The vital capacity, in other words, was within normal limits both before and after the test, and, after the latter time, the patient still exhibited a tachypnea and tachycardia. The venous pressure was measured in six of these patients by direct puncture of the right antebrachial vein, both before and immediately after exercise. It was found to average 6.6 cm. of water before, and 6 cm. of water directly after exercise. Both of these values are within normal limits. The circulation time (arm-

to-tongue) was determined by the injection of calcium gluconate into six patients with NCA, before, and two minutes after, the cessation of exercise. The average time of circulation before and after exercise was 12 and 10.5 seconds, respectively. Thus, it was found that despite the tachypnea and tachycardia of the average patient with NCA after performing the standard exercise test, there was no indication from these measurements that cardiac failure or inefficiency of any perceptible degree was present.

TABLE II. THE VITAL CAPACITY, VENOUS PRESSURE, AND CIRCULATION TIME OF PATIENTS WITH NCA BEFORE AND AFTER A STANDARD EXERCISE TEST

CASE	BEFORE TEST			AFTER TEST		
	VITAL CAPACITY*	VENOUS PRESSURE†	CIRCULATION TIME‡	VITAL CAPACITY	VENOUS PRESSURE	CIRCULATION TIME
1	2.25	5.5	12	2.25	4.0	10
2	2.70	10.0	12	2.70	11.0	10
3	2.50	5.7	12	2.55	6.2	11
4	2.00	2.0	13	2.14	3.0	12
5	2.40	9.5	12	2.45	6.0	10
8	1.80	7.0	13	1.70	6.0	10
9	2.53	—	—	2.11	—	—
Average	2.31	6.6	12	2.27	6.0	10.5

*Liters of air per square meter of body surface.

†Cubic centimeters of water.

‡Seconds.

3. *The Pulse and Respiratory Rate During Special Exercise Test.*—A simple test was devised which consisted of a small fixed pulley, over which a cord, fastened to an 8-pound weight, was suspended. The patient was seated and asked to raise and lower the weight over a distance of 10 cm., fifty times a minute, by pulling and releasing the cord. The pulse and respiratory rates were obtained at the end of 30, 60, 120, 180, 240, and 300 seconds. Before the patient was allowed to perform this test, however, he first watched others do it. He then performed the test three times on three different days; the last test was used for the calculations shown in Table III. The procedure was adopted in order to eliminate, as far as possible, any anxiety or nervousness on the part of the patient while performing the test. It was noted repeatedly that many patients with NCA began to breathe fast, with corresponding tachycardia, when they first attempted this simple exercise. Indeed it is felt strongly that much of the work

TABLE III. THE RESPIRATORY AND PULSE RATE OF PATIENTS WITH NCA AND NORMAL ADULTS BEFORE AND DURING A SPECIAL EXERCISE TEST

BEFORE TEST			DURING TEST									
CASE	RESP.	PULSE	30 SECONDS		60 SECONDS		120 SECONDS		180 SECONDS		240 SECONDS	
			RESP.	PULSE	RESP.	PULSE	RESP.	PULSE	RESP.	PULSE	RESP.	PULSE
Patients With NCA												
B1	20	80	20	96	22	90	22	90	22	102	24	108
B2	22	88	20	102	24	108	26	102	24	112	24	115
B3	18	78	20	98	20	102	22	98	24	102	24	102
B4	19	78	20	90	20	102	20	98	20	102	22	102
B5	21	60	22	66	24	72	22	84	22	84	22	—
B6	22	88	22	102	22	104	24	106	22	120	23	120
B7	18	78	18	84	20	90	22	96	24	96	22	—
B8	19	88	18	100	20	96	20	102	22	102	22	120
Average	20	80	20	92	22	96	22	97	23	103	24	111
Normal Adults												
C1	18	78	20	96	22	96	24	90	24	92	24	98
C2	21	78	20	94	24	104	24	104	22	108	22	114
C3	19	80	22	90	22	98	24	102	26	108	24	114
C4	16	72	18	76	20	84	20	84	22	88	24	94
C5	22	78	20	80	24	86	22	90	24	96	22	106
C6	21	84	22	96	22	96	24	96	24	106	24	106
Average	20	78	20	89	22	94	23	94	24	100	23	105

previously done on the exercise tolerance of the patient with NCA may be misleading because the element of anxiety was not eliminated during such studies. It is a simple point, but one important enough to invalidate any assay of exercise tolerance, if not kept in mind.

Eight patients with NCA and six normal adults were given the test. The results, as shown in Table III, indicate that there was no significant difference in the hemodynamic response of the patient with NCA and that of the normal individual, as judged by pulse and respiration changes during the exercise. The average pulse rate of the patients with NCA increased from 80 to 111 beats per minute at the end of 240 seconds of exercise (an increase of 35.8 per cent), and the average pulse rate of the normal individuals, at the end of the same period, increased from 78 to 105 beats per minute (an increase of 34.6 per cent). The average respiratory rate in both groups was found to remain below 24 per minute during the entire test.

These observations indicate rather conclusively that, if the emotional tachypnea of the patient with NCA is eliminated during an exercise test, no cardiac dysfunction will be observed. Even in the standard test, in which no effort was made previously to acquaint the patient with it, and in which the patient with NCA exhibited persisting tachypnea and tachycardia, evaluation of the cardiac efficiency by measurements of the vital capacity, venous pressure, and circulation time revealed no defect.

It is of interest in this connection that Fraser and Wilson,¹⁶ in commenting on the response of the patient with NCA to exertion, wrote, "These patients appear to differ from healthy men only in that a stimulus such as excitement or emotion produces an unusually large response." Jones and Lewis¹⁷ also observed, "—it is not effort but the situation in which effort may be required and the emotional attitude of the man toward this situation that are often the significant factors." Certainly our own observations are in complete agreement with the views of these men.

E. EXPERIMENTAL OBSERVATIONS CONCERNING THE CARDIOVASCULAR MANIFESTATIONS

1. *Dyspnea*.—Although forty-seven patients with NCA (94 per cent) complained of breathlessness after relatively slight exertion, it was found, as described above, that, when a group of these individuals performed work without any element of concomitant anxiety or emotional tension of any sort, they did not experience dyspnea sooner, or more severely, than the normal person doing the same work. This last observation, together with the lack of signs of cardiac insufficiency in the uncontrolled exercise test described previously, indicated that the respiratory distress of these individuals was not of cardiac origin.

2. *Precordial Pain*.—Forty-four patients with NCA (88 per cent) complained of intermittent precordial pain. This particular symptom, perhaps more than any other, has been responsible for the interest of the cardiologist in neurocirculatory asthenia. Some writers,^{18, 19} however, have considered the symptom as imaginary or the result of the patient's preoccupation with his heart. Wood¹³ recently has presented very good evidence that precordial pain in many instances may be due to respiratory dysfunction.

In the present studies, it was found that there were actually *two* separate and distinct types of precordial pain which might be experienced by patients with NCA. It was also discovered that they were not due to the same causes. It is probable that needless confusion has existed in the past concerning the nature and cause of the precordial pains occurring in the patient with NCA because of the failure to differentiate these two distinct types.

The most common form of pain (experienced by twenty-four patients with NCA (58 per cent) was a sharp, piercing, transient one that began at the left nipple and penetrated deep into the chest. The intensity was most severe, although the pain rarely persisted over five minutes. The patients described this pain as a sensation of being stabbed, torn, or cut. Eight of the twenty-four patients stated that, either preceding or concomitant with the perception of this pain, they were aware of their hearts beating irregularly. The remaining sixteen patients stated that they were unaware of any irregularity of rhythm, but they did observe that the heart began to beat extraordinarily forcefully, either before or during the attack of precordial pain. Because each of the patients thus insisted that their pain was preceded or accompanied by perceptible changes in either the rhythm or force of cardiac contraction, it was suspected that this type of precordial pain was cardiac in origin.

Accordingly, the susceptible patients were instructed to report for examination immediately at the onset of their precordial pain. Because they were hospitalized patients, thirteen of them were examined almost at the first twinge of pain. It was found on physical and electrocardiographic examination that seven of these patients exhibited some type of transient arrhythmia at the time of the onset of precordial pain (ventricular extrasystoles, 3; auricular paroxysmal tachycardia, 2; wandering auricular pacemaker, 1; and auricular flutter, 1). The remaining six patients were found to have normal electrocardiograms, but the clinical examination revealed that the hearts of all six were pounding very forcefully against the chest wall. Of even greater interest was the observation that ten of these thirteen patients, during their attack of precordial pain, also exhibited cold, wet hands with accentuated tremor, profuse axillary perspiration, and dilatation of the pupils. These extracardiac findings indicated that a nervous discharge had occurred, in addition to the cardiac symptoms and signs. These patients were carefully observed, and it was found that the precordial pain did not persist after the disappearance of the observed arrhythmia and the excessive pounding of the heart against the chest wall.

These findings made it clear that the cause of the sharp, excruciatingly severe, precordial pain was of cardiac origin. It was also obvious that, in the majority of cases, the cardiac changes were but the cardiovascular manifestations of a nervous discharge, strongly suggestive of an excitation of the sympathetic nervous system.

The second type of precordial pain experienced by many patients with NCA was a dull, aching, persistent pain confined, but not sharply limited, to a wide area of the left side of the chest, with the left nipple usually as its center. It was invariably produced by exercise but usually appeared several minutes, to several hours, after the performance of any particular exertion. It was felt by many patients for many hours, contrasting sharply to the sharp type of pain previously described, which rarely lasted over five minutes. It is believed that this is the type of pain described by Wood,¹² who thought it was due to respiratory dysfunction. In data to be published later, sufficient evidence was accumulated to confirm his theory concerning the pathogenesis of this type of precordial pain. It should be mentioned, however, that several patients with NCA in the present series were wont to experience both types of pain at intervals.

3. *Palpitation*.—Forty-seven patients (94 per cent) stated that they had experienced bouts of palpitation. Twenty were examined during hospitalization, at a time when they experienced this sensation. Four were found to have ventricular extrasystoles, and the remaining sixteen patients were observed to have

the pounding of the heart against the chest wall, previously observed in many of the patients with NCA who complained of precordial pain of the sharp, transient variety. As a matter of fact, six of these twenty patients also complained of the sharp precordial pain at the time they experienced palpitation. Fifteen of the twenty patients also showed signs of the nervous discharge.

4. *Changes in the Temperature and Color of the Extremities.*—The cold, cyanotic extremities of the patient with NCA have been described often by various observers.^{12, 13} The condition has been thought¹³ to be due to arteriolar vasoconstriction. Although forty-five patients with NCA (92 per cent) in the present series exhibited such changes in their extremities at some time during hospitalization, it was not a permanent phenomenon. Rather, it was a transient, episodic condition, associated with the characteristic nervous discharge which has been described as preceding or accompanying the other cardiovascular manifestations of the syndrome. Between these episodes and always during sleep, the skin of the patient with NCA appeared normal, both in temperature and color.

F. THE EFFECTS OF VARIOUS DRUGS ON THE CARDIOVASCULAR SYSTEM

The majority of investigators who have made studies concerning the etiology and pathogenesis of neurocirculatory asthenia have been impressed with the striking similarity of many of its manifestations to those following an excitation of the sympathetic nervous system. Fraser and Wilson¹⁶ were the first observers who stressed the involvement of the autonomic nervous system in the pathogenesis of the syndrome. Kessel and Hyman²⁰ stressed the presence of autonomic imbalance in the production of neurocirculatory asthenia but did not attempt to correlate their physiologic findings with anatomic elements of the autonomic nervous system. Cannon²¹ also pointed out the essential similarity of the syndrome of NCA to the rage or fear reaction occurring in the experimental animal after excitation of the sympathetic nervous system. Despite this admitted involvement of the autonomic nervous system in the pathogenesis of neurocirculatory asthenia, however, the exact locus of its conjunction with, or participation in, the elements making up the entire syndrome remains unknown. For, although the somatic elements of the disease are mediated obviously by the autonomic nervous system, there is little reason to believe that the entire syndrome occurs because of some peripheral disturbance in this latter segment of the nervous organization.

In an effort to investigate the role of the autonomic nervous system in the pathogenesis of this disease, patients with NCA were given various drugs which acted on the peripheral terminations of this system. In addition, they were given two drugs, caffeine and benzedrine, which are known²² to exert their principal effects on the higher centers of the central nervous system. It was hoped, by such experimentation, that not only the portion of the autonomic system involved in these patients might be determined, but also at what level the function of this system was hyperactive or deranged.

The autonomic effector drugs (epinephrine and physostigmine) were administered to patients with NCA when they exhibited a minimum of cardiovascular manifestations. The anticholinergic drugs (atropine and scopolamine) were given, however, when the patients displayed a marked accentuation of symptoms and signs. Caffeine and benzedrine were given during quiescent periods of the syndrome. These periods (according to the drug employed) were chosen because it would be difficult, for example, to determine the role of epinephrine in a patient with NCA who already was exhibiting maximal signs of the

TABLE IV. THE RESPONSE OF THE PATIENTS WITH NCA TO THE ADMINISTRATION OF VARIOUS DRUGS

CASE	BEFORE ADMINISTRATION							AFTER ADMINISTRATION								
	RESP.	PULSE	TREMOR	PERSPIRA- TION	SKIN (HANDS)	CARDIAC ARRHYTH- MIA	FORCEFUL HEART BEAT	PRE- CORDIAL PAIN	RESP.	PULSE	TREMOR	PERSPIRA- TION	SKIN (HANDS)	CARDIAC ARRHYTH- MIA	FORCEFUL HEART BEAT	PRE- CORDIAL PAIN
A. Administration of Epinephrine (0.5 Mg.) by Intramuscular Injection																
a. Patients With NC.1																
R. G.	20	86	+	+	Warm	Absent	Absent	Absent	20	100	+++	+++	Very cold	Absent	Present	Present
C. N.	18	100	+++	++	Cool	Absent	Absent	Absent	18	112	+++	+++	Very cold	Absent	Present	Present
J. C.	20	84	+	+	Warm	Absent	Absent	Absent	20	108	+++	+++	Very cold	Absent	Present	Absent
H. P.	20	112	++	++	Warm	Absent	Absent	Absent	18	122	+++	+++	Very cold	Absent	Present	Absent
Average	20	96							19	111						
b. Normal Adult Controls																
T. T.	18	78	0	0	Warm	Absent	Absent	Absent	20	110	+++	+	Warm	Absent	Present	Present
R. S.	20	82	0	0	Warm	Absent	Absent	Absent	20	108	+++	0	Warm	Absent	Present	Absent
H. Z.	20	80	0	0	Warm	Absent	Absent	Absent	20	105	+++	0	Warm	Absent	Present	Absent
Average	19	80							20	107						
B. Administration of Physostigmine (1 Mg.) by Intramuscular Injection																
Patients With NC.1																
H. P.	20	84	++	++	Cold	Absent	Absent	Absent	20	84	++	++	Warm	Absent	Absent	Absent
J. C.	20	88	+	+	Warm	Absent	Absent	Absent	18	88	+	+	Warm	Absent	Absent	Absent
E. R.	18	84	+++	+++	Warm	Absent	Absent	Absent	20	84	+++	+++	Warm	Absent	Absent	Absent
R. G.	20	88	+	+	Warm	Absent	Absent	Absent	18	86	++	++	Warm	Absent	Absent	Absent
Average	20	86							19	86						
C. Administration of Atropine (1.5 Mg.) by Subcutaneous Injection																
Patients With NC.1																
R. S.	24	88	+++	+++	Very cold	Absent	Present	Present	24	120	+++	0	Warm	Absent	Present	Present
R. G.	22	100	+++	+++	Very cold	Absent	Absent	Absent	22	110	+++	0	Warm	Absent	Present	Absent
H. P.	26	96	+++	+++	Very cold	Absent	Present	Present	28	118	+++	0	Warm	Absent	Present	Present
D. W.	24	96	+++	+++	Very cold	Present*	Present	Absent	22	140	+++	0	Warm	Absent	Present	Absent
Average	24	95							24	122						
D. Administration of Scopolamine (0.6 Mg.) by Subcutaneous Injection																
Patients With NC.1																
E. R.	24	94	+++	+++	Very cold	Absent	Present	Absent	24	92	+++	+++	Warm	Absent	Present	Absent
H. P.	22	88	+++	+++	Very cold	Absent	Present	Present	22	94	+++	+++	Warm	Absent	Present	Present
E. K.	23	96	+++	+++	Very cold	Absent	Present	Present	24	98	+++	+++	Warm	Absent	Present	Absent
Average	23	93							23	95						

E. Administration of Caffeine (500 Mg.) by Oral Ingestion									
a. Patients With NCA									
D. W.	20	76	++	+	Warm	Absent	Absent	30	96
D. C.	20	88	++	+	Warm	Absent	Absent	24	84
W. B.	24	86	++	+	Warm	Absent	Absent	30	112
E. R.	16	74	++	+	Warm	Absent	Absent	28	90
H. P.	20	86	+++	+	Cool	Absent	Absent	24	96
M. N.	20	84	++	+	Warm	Absent	Absent	22	108
Average	20	82	+	+	Warm	Absent	Absent	26	98
b. Normal Adult Controls									
E. H.	18	88	0	0	Warm	Absent	Absent	16	72
R. C.	20	60	0	0	Warm	Absent	Absent	20	60
T. S.	18	88	0	0	Warm	Absent	Absent	20	78
Average	19	79	0	0	Warm	Absent	Absent	19	70
F. Administration of Benzadrine (10 Mg.) by Oral Ingestion									
a. Patients With NCA									
R. S.	20	85	++	+	Warm	Absent	Absent	20	108
H. E.	20	64	++	+	Warm	Absent	Absent	32	98
D. C.	26	76	++	+	Warm	Absent	Absent	28	79
H. P.	20	91	++	+	Warm	Absent	Absent	32	109
F. M.	—	90	++	+	Warm	Absent	Absent	—	95
R. G.	20	89	++	+	Warm	Absent	Absent	28	106
Average	21	83	++	+	Warm	Absent	Absent	28	99
b. Normal Adult Controls									
E. Y.	18	87	0	0	Warm	Absent	Absent	18	86
W. R.	20	60	0	0	Warm	Absent	Absent	20	69
W. W.	20	75	0	0	Warm	Absent	Absent	20	76
Average	19	74	0	0	Warm	Absent	Absent	19	77
*Ventricular extrasystoles.									

syndrome before medication. Likewise, the use of anticholinergic drugs during a quiescent period of the syndrome would be without value in assessing the role of the parasympathetic nervous system in the production of neurocirculatory asthenia. These precautions are extremely important in dealing with a disease so episodic in character, and some of the conflicting views concerning the results following the administration of various autonomic drugs may have arisen because of the failure to ascertain the exact status of the patient before these drugs were given.

1. *The Administration of Epinephrine.*—Inspection of Tables IV, A, shows clearly that the intramuscular injection of epinephrine produced no greater changes in the patient with NCA, for the most part, than in the normal individual. In both groups, the injection was followed by increase in pulse rate and force of cardiac contraction. Increase in the force of the heart beat by this procedure produced the sharp type of precordial pain in two patients with NCA and in one normal individual. The only real difference observed was the occurrence of cold, wet hands in the patients with NCA, which was observed to occur only after they had begun to feel anxiety about the forceful contraction of the heart making it doubtful that the epinephrine directly evoked the changes in the peripheral blood vessels and sweat glands. The pre-existing tremor of the patients with NCA was seen to increase, but all normal adults also exhibited a tremor following the injection of the drug.

2. *The Administration of Physostigmine.*—The intramuscular injection of physostigmine into four patients with NCA (Table IV, B) during a relatively quiescent period of the syndrome, evoked no essential change in the pulse rate, the degree of perspiration, or in the color and temperature of the upper extremities. The tremor did not increase in any patient. It appeared, then, that the cardiovascular apparatus of the patient with NCA was not hypersusceptible to this cholinergic drug. By inference, it would seem that these patients were also not unduly sensitive to parasympathetic discharge.

3. *The Administration of Atropine.*—The subcutaneous injection of atropine into four patients with NCA (Table IV, C) during exacerbations of symptoms and signs, had no effect in inhibiting the increase in respiratory rate or tremor of the extremities. The cardiac rate was increased in even greater degree. Atropine, however, did abolish the excessive perspiration and the coldness of the hands. It should be mentioned in this connection that, although perspiration is a function of the sympathetic nervous system, the effector drug actually causing the increased perspiration has been found to be acetyl choline.²² This makes it clear that the abolition of excessive perspiration by the injection of atropine does not indicate that a previously increased parasympathetic discharge was present in these patients.

4. *The Administration of Scopolamine.*—The subcutaneous injection of scopolamine into three patients with NCA, during exacerbations of the disease, was followed (Table IV, D) by the disappearance of previously cold extremities. The other manifestations of the syndrome were unchanged after injection.

5. *The Administration of Caffeine.*—When caffeine citrate was given orally to six patients with NCA during quiescent periods of their illness and to three normal young adults (for control purposes), a marked effect was observed only in the patients with NCA (Table IV, E). Five of the six patients exhibited an increase in the pulse rate (average increase: 16 beats per minute). Each of the six patients showed an increase in respiratory rate (average increase: 6 respirations per minute). The tremor also became accentuated, and the hands

of all patients with NCA became wet and cold. The impact of the heart against the chest wall was observed to increase in intensity in all patients and three patients with NCA complained of the sharp, transient type of precordial pain. One patient had a transient arrhythmia, due to the onset of ventricular extrasystoles. As mentioned, the normal individuals showed no significant change in pulse or respiratory rate, in rhythm, or force of cardiac contraction, or in degree of perspiration.

6. *The Administration of Benzedrine.*—Benzedrine sulphate produced dramatic changes when given to six patients with NCA, but there were no perceptible changes in the normal individuals to whom it was given. Thus (Table IV, *F*) the average pulse rate of the six patients with NCA increased from 88 to 99 beats per minute, and the respiratory rate accelerated from 21 to 28 breaths per minute. Each of the six patients complained of palpitation, and four experienced the sharp, transient type of precordial pain. The hearts of all patients with NCA were observed to contract much more forcefully after the administration of benzedrine and, in two patients, ventricular extrasystoles followed the ingestion of the drug. The hands of all patients, regardless of their state prior to the administration of benzedrine, became cold and wet. Two patients also exhibited purplish mottling of the skin of their extremities. Axillary perspiration increased in all patients following the ingestion of benzedrine.

DISCUSSION

From the preceding observations, it must be assumed that the heart of the patient with NCA is basically sound both in structure and function. If, occasionally at rest, and always during effort associated with emotional activity, this type of patient experienced dyspnea, palpitation, and precordial pain, and exhibited tachypnea, forceful beating of the heart, arrhythmia, and coldness of the extremities, there was sufficient evidence also that these cardiovascular symptoms and signs were preceded or accompanied by a nervous discharge which seemed to bear a causal relationship to the onset of the cardiovascular dysfunction observed.

Thus, it was found that the real mechanism responsible for the occurrence of not only the cardiovascular manifestations, but also of the other somatic manifestations of the disease, was the episodic, frequently spontaneous occurrence of this nervous discharge. The cardiac and extracardiac characteristics, the close relationship to emotion, and the experimental simulation of these signs and symptoms in the normal individual by the administration of excessive amounts of epinephrine, indicated that the nervous discharge was sympathetic in nature. The inability to reproduce an exacerbation of the syndrome in the patient with NCA by the administration of cholinergic drugs, further confirmed this probability.

However, the peripheral portion of the sympathetic nervous system in the patient with NCA was not found to be unduly sensitive to epinephrine, which suggested that the abnormality in this portion of the autonomic nervous system was not a peripheral one. The production of the same type of nervous activity by emotional activity and by the administration of caffeine and benzedrine (drugs having their chief effect on the higher centers of the central nervous system²²) indicated that there was stimulation of the sympathetic nervous system at its central point. Since the hypothalamus has been described²³ as the locus of this point, it would appear that this portion of the brain in the patient with NCA was unduly responsive to emotional activity or to the administration of the

aforementioned drugs. The presence of fever in many patients with NCA¹ together with other symptoms and signs previously described² further suggests hypothalamic dysfunction in this illness.

This incrimination of the hypothalamic area of the brain in the pathogenesis of neurocirculatory asthenia is not to be construed as a belief that hypothalamic dysfunction is responsible for the genesis and pathogenesis of the entire syndrome. It is believed, however, that the evidence is strong for the assumption that this portion of the brain is responsible for the emergence of the somatic manifestations seen in this disease. It should be pointed out, in this connection, that neurocirculatory asthenia is intimately associated with emotion and the latter, in turn, has close relationship with the hypothalamus.

CONCLUSIONS

1. The cardiovascular manifestations of neurocirculatory asthenia were studied in fifty patients.

2. The heart of the patient with NCA was found to be normal in size, structure, and function at rest and also during effort if unaccompanied by emotional activity.

3. Changes in the rate, rhythm, and force of cardiac contractions were observed in the patient with NCA to be preceded by, or associated with, excitation of the sympathetic nervous system. This phenomenon was observed during a natural exacerbation of the syndrome or following the administration of suitable drugs.

4. Evidence was obtained which suggested that the excitation of the sympathetic nervous system, preceding or associated in a causal fashion with the cardiovascular manifestations of neurocirculatory asthenia, resulted from hypothalamic discharge.

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PULMONARY STENOSIS WITH INTACT INTERVENTRICULAR SEPTUM

REPORT OF ELEVEN CASES

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STENOSIS of the pulmonary valve is encountered quite frequently in infants and young adults with congenital heart disease and is usually associated with the other three components of the tetralogy of Fallot, namely, interventricular septal defect, transposition of the aorta, and hypertrophy of the right ventricle. In Maude Abbott's^{1, 2} series of 1,000 cases of congenital heart disease, pulmonary stenosis was associated with an interventricular septal defect in eighty-five cases and, in thirty-four of these, the foramen ovale was also patent. However, in twenty-five other cases, she found pulmonary stenosis associated with an intact interventricular septum; sixteen of these demonstrated patency of the foramen ovale. Pulmonary atresia is not considered, because it is of little clinical significance and is usually incompatible with life. Thus, according to Abbott's findings, at least two patients in seven with pulmonary stenosis will not have a ventricular septal defect, but this has not been adequately recognized in general or, even as a rule, by cardiologists, themselves.

Interest in pulmonary stenosis with intact interventricular septum was stimulated recently by the observation of three such cases. The clinical diagnosis was in error in two of the cases while, in the third case, a correct diagnosis was made. Search of the autopsy protocols of the Boston City Hospital, Massachusetts General Hospital, and Children's Hospital revealed a total of eleven cases in which pulmonary stenosis was not associated with a ventricular septal defect. An analysis of these cases with the pertinent physical and anatomic findings, together with the available electrocardiograms and roentgenograms, form the basis for this report. A few remarks concerning etiology likewise seem appropriate.

CASE 1 (R. J., 39805).—The patient was a 12-year-old boy, first seen in the Outpatient Department of the Massachusetts General Hospital in April, 1937, when he was referred from the Children's Hospital. In March, 1929, at the age of 4 years and 4 months, he had been examined in the Children's Hospital, at which time some cyanosis of the fingers and lips, but no clubbing of the fingers or toes, was observed. The blood pressure at that time was 110/60.

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The hemoglobin was 55 per cent and the red blood cell count was 4.08 million per cubic millimeter. His mother had noted some cyanosis of the face and internal strabismus since the age of 3 years. In October, 1930, a definite bulge was noted in the precordial region, and he was observed to be somewhat dyspneic on exertion. In April, 1932, his hemoglobin was 95 per cent; his red blood cell count was 5.7 million and his white blood cell count was 13,000 per cubic millimeter. The diagnosis of the tetralogy of Fallot was thought to explain best the congenital anomaly of the heart. In May, 1936, an electrocardiogram was taken which revealed evidence of marked right ventricular enlargement. He had been treated at the Massachusetts Eye and Ear Infirmary, from the time he was 8 until he was 12 years of age, with optical glasses for internal strabismus, with good results.

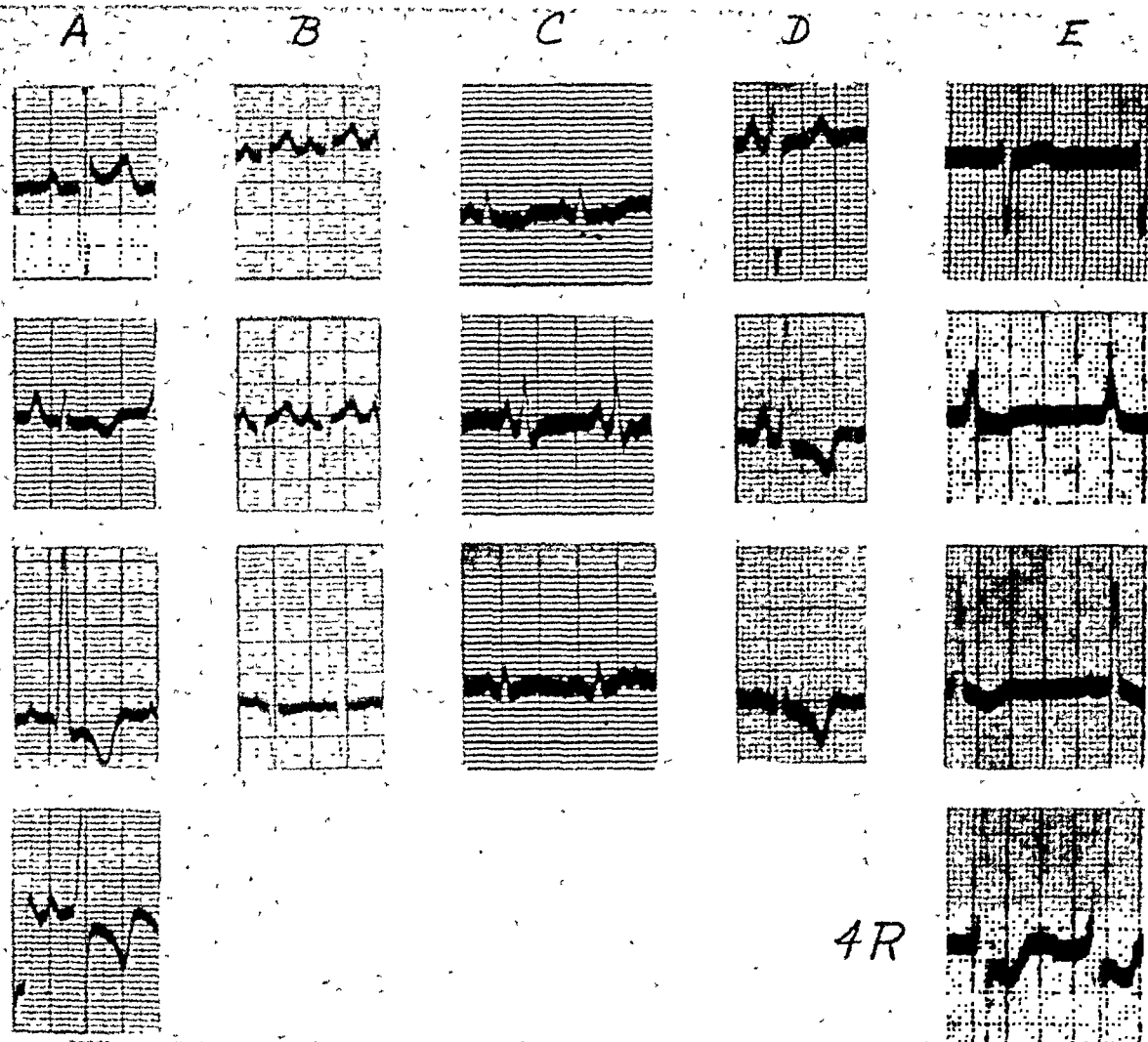


Fig. 1.—The electrocardiograms of four patients with pulmonary stenosis. A, Case 1. The tracings made in 1937 and 1941 were essentially the same. The high degree of right axis deviation, inversion of T waves in Leads II, III, and IVF, and prominent P waves should be noted. B, Case 2. The high degree of right axis deviation is apparent; the Q waves in Leads II and III are prominent and measure 6 millimeters. The T wave in Lead III is isoelectric. C, Case 4. There is no evidence of right ventricular strain in this tracing. It is, however, similar to the changes seen in some cases of pellagra.¹¹ The short P-R interval and low T waves should be noted; the T wave in Lead I is slightly inverted. D (April 8, 1937) and E (May 6, 1941), Case 9. The tracing is quite similar to that of Case 1. Auricular fibrillation developed shortly before death (E).

The physical examination revealed a small, intelligent, blond male, exhibiting mild cyanosis of the lips, cheeks, and fingers, with slight clubbing of the fingers. The left border of dullness was 8 cm. to the left of the midsternal line in the fifth intercostal space, 1 cm. beyond the midclavicular line. There was a moderately loud, but not intense, rough systolic murmur in the pulmonic area, with a very slight thrill; the murmur was heard also, less loudly, at the apex. The second sound at the pulmonic area was of good quality and was equal in intensity to the aortic second sound. The blood pressure was 95/70. The electro-

CURRENS ET AL.: PULMONARY STENOSIS

deviation and prominent P waves. The T waves in Leads II, III, and IVF were inverted (Fig. 1, A). The x-ray film of the chest demonstrated enlargement of the heart, most striking at the base of the heart, with some prominence of the pulmonary artery (Fig. 2, A). Because of the appearance of the heart by x-ray examination, which showed a prominent pulmonary artery, the diagnosis of Eisenmenger's complex (ventricular septal defect, dextro-position of the aorta, dilated pulmonary artery, and a large right ventricle) was made.

In October, 1939, the cyanosis and clubbing of the fingers were little changed from that observed previously. However, by July, 1941, the cyanosis had become greater, though still moderate in degree, there was noted marked prominence of the precordium, and the pulmonary second sound was thought to be less loud than it normally is for a person his age.

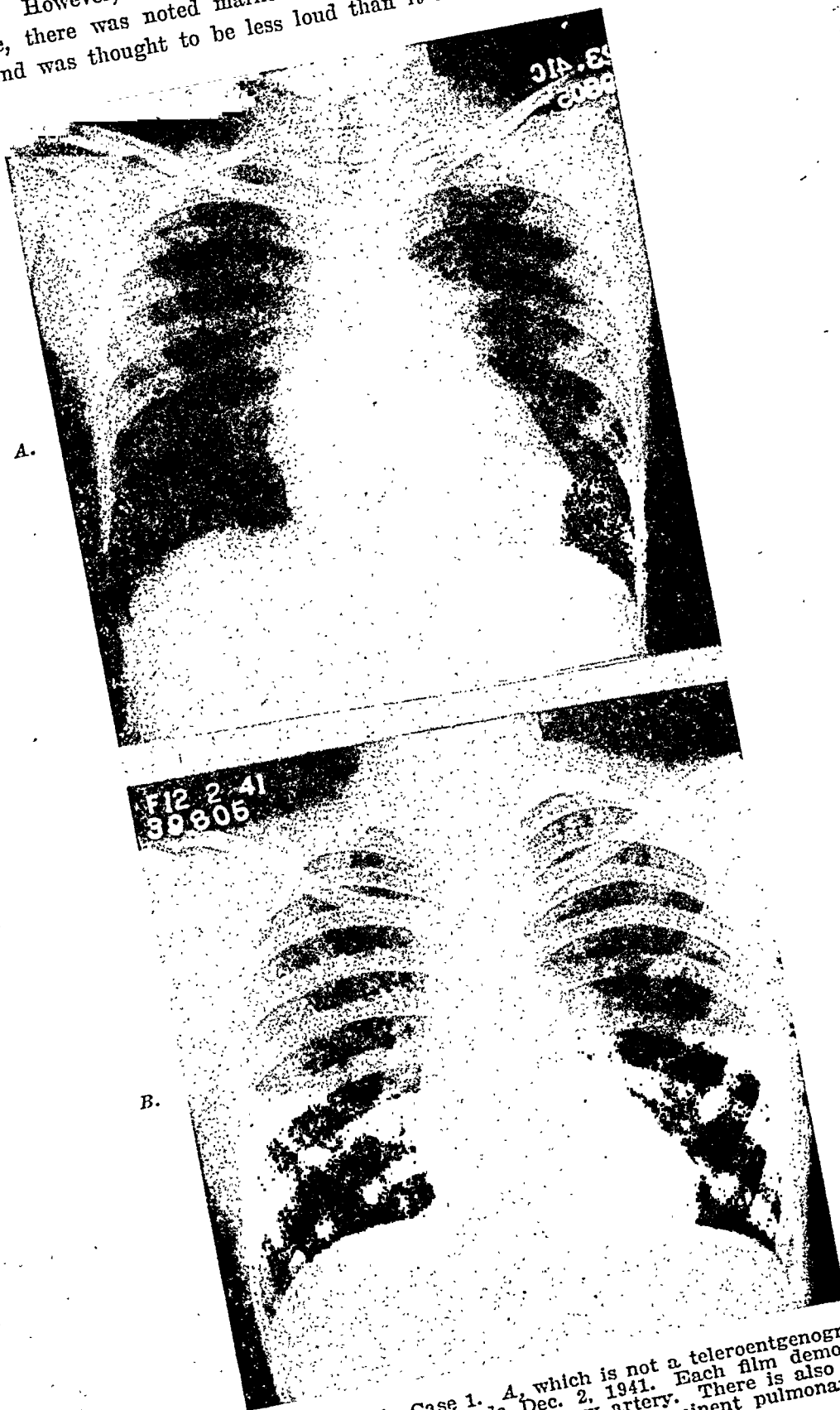


Fig. 2.—Roentgenograms in Case 1. A, which is not a teleroentgenogram, was made July 23, 1941. B is a teleroentgenogram made Dec. 2, 1941. Each film demonstrates slight cardiac enlargement and prominence of the pulmonary artery. There is also a partial left pneumothorax present in the lower film. Because of the prominent pulmonary artery, the diagnosis of Eisenmenger's complex was made.

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In December, 1941, the patient was brought to the hospital because of severe pain in the left side of the chest, followed by nausea and vomiting. The x-ray film of the chest (Fig. 2, *B*) demonstrated a partial left pneumothorax. The pain subsided after one day, and he returned home. In April, 1942, the cyanosis and clubbing were described as marked. The patient was clearly undersized for his age, weighing 84 pounds and measuring 5 feet, 4 inches in height. A slight venous pulse was noted in the neck at this time. In August, 1942, the hemoglobin was 22.7 Gm., and the red blood cell count was 8.65 million per cubic millimeter. In September, 1942, he was mostly confined to bed, after several episodes of fainting, which were followed by moderate dyspnea. He was finally admitted to another hospital where he died, with moderate respiratory failure, in November, 1942. The clinical diagnosis was congenital heart disease, Eisenmenger's complex.

Autopsy Findings.—Anatomic diagnosis: (1) Congenital cardiac anomaly: (a) fusion of the cusps of the pulmonic valve, with marked stenosis; and (b) insufficiency and patency of the foramen ovale. (2) Cardiac hypertrophy, the heart weight being 380 grams. (3) Platelet thrombus on the pulmonic valve. (4) Chronic passive congestion of liver, spleen, pancreas, and kidneys.

The heart was globular in shape; the right side appeared larger than the left, and the apex was formed by the right ventricle. The foramen ovale was patent and admitted a 1-cm. probe with ease (Fig. 3, *A*). The right ventricular wall measured 1.5 cm. in thickness, as compared with 1.3 cm. for the wall of the left ventricle. The valves were normal except for the pulmonary valve, whose cusps were completely fused (Fig. 3, *B*). The orifice was oval and measured 6 mm. in diameter. Attached loosely, at the right side of the opening, was an irregularly shaped friable thrombus, 6 mm. in length. The pulmonary artery was moderately dilated, the ductus arteriosus was closed, and the interventricular septum was closed.

Microscopic examination demonstrated that the small thrombus on the pulmonary valve consisted largely of platelets and fibrin. There was no evidence of an increase in connective tissue in the liver, but there was marked congestion of the blood vessels.

CASE 2 (L. M., 401880).—A 3-month-old female infant entered the Massachusetts General Hospital on May 5, 1943, because of convulsions. Two weeks prior to entry, while lying in the crib crying, the patient was observed to stiffen suddenly for a moment and then lie completely limp, breathing stertorously. This occurred again the day of admission. The patient was the victim of an arduous delivery which lasted four days and was finally terminated by rotation and extraction with forceps. The patient had had a face presentation and the mother, a contracted pelvis. The infant weighed 7½ pounds at birth, and was said to be cyanotic; resuscitation was accomplished with difficulty. However, since birth, no cyanosis, dyspnea, or cough had been noted.

The physical examination revealed an infant who showed little interest in her surroundings. The eyes were directed downward to the left and the upper extremities were trembling. The pupils were equal and reacted to light. The heart was enlarged to the left; the left border of dullness measured 2 cm. beyond the midclavicular line. A loud, harsh systolic murmur was heard over the precordium, maximal at the pulmonary area, and was also heard over the back. The second heart sound in the pulmonary area was present, but diminished in intensity. The blood pressure was 90/40. No cyanosis or clubbing was present. The abdomen was normal and the deep tendon reflexes were present. Moderate talipes varus was present bilaterally.

The laboratory examination revealed a hemoglobin of 14.2 Gm. The erythrocytes numbered 4.40 million and the leucocytes 13,400 per cubic millimeter. The blood smear and differential count were not remarkable. The urinalysis was normal. A tourniquet test was negative and the bleeding time was four minutes. The prothrombin time was 17 seconds (with a normal of 18 seconds). An x-ray film of the skull revealed evidence of moderate bulging of the fontanels. The x-ray examination of the chest revealed a heart which was moderately enlarged, as illustrated in Fig. 4. The electrocardiogram (Fig. 1, *B*) showed normal rhythm, at a rate of 150 to 160 per minute. The P-R interval measured 0.12 seconds, the Q_2 and Q_3 deflections measured 6 mm., and there was marked right axis deviation.

A cerebral "ventricular" tap was attempted on the day of entry; it revealed grossly bloody fluid with an erythrocyte count of 500,000 per cubic millimeter and xanthochromic supernatant fluid after centrifuging. The total protein of the supernatant fluid was 2,160 mg. per cent. Another "ventricular" tap, attempted the following day, yielded similar results. A lumbar puncture on May 8, 1943, revealed grossly bloody fluid with xanthochromic supernatant fluid. However, the fluid removed by lumbar puncture became less bloody and, by May 18, the fluid contained only 20 erythrocytes per cubic millimeter, and the total protein was

22 mg. per cent. The pressure, however, was elevated, ranging from 250 to 400 cm. of water, as the initial pressure, and this elevation continued, in spite of lumbar punctures every one or two days. On June 2, a combined lumbar and "ventricular" tap revealed grossly bloody fluid from the "ventricles" with xanthochromic fluid, while the fluid from the spinal puncture was clear. Dye, injected into the "ventricular" needle, failed to appear in the lumbar region. On July 8, bilateral frontal exploration with Burr holes was done, and bilateral subdural fluid was obtained. The condition of the patient changed little and, on July 14, an attempt was made to remove the subdural sacs, but the patient stopped breathing during the operation.

A.



B.



Fig. 3.—The heart in Case 1. A, The right auricle and ventricle are open and the marked hypertrophy of the right ventricle can be seen. The arrow on the left is placed through the patent foramen ovale, while the arrow on the right is placed through the stenotic pulmonary valve. B, A close view of the pulmonary valve, demonstrating the fusion and scarring of the pulmonary valve leaflets and a small vegetation attached to the superior surface. Moderate dilatation of the pulmonary artery, distal to the valve, is also evident.

The clinical diagnoses were as follows: (1) subdural hematoma, bilateral; (2) hydrocephalus; (3) cyst of the corpus callosum; (4) talipes varus; and (5) interventricular septal defect.

Autopsy Findings.—Anatomic diagnosis: (1) bilateral subdural hematoma; (2) congenital heart disease with pulmonary stenosis; and (3) previous operations: (a) bilateral frontoparietal exploratory trephining, and (b) right craniotomy, with removal of hematoma and its membrane.

The heart weighed 50 grams, and there was prominence of the right ventricle. The right ventricular wall measured 9 mm., and the left ventricular wall measured 7 mm. in thickness. The columnae carneae were hypertrophied in the right ventricle. The foramen ovale was patent, but not dilated, and there was no evidence that any appreciable amount of blood had

A.



B.



FIG. 4.—A, The roentgenogram in Case 2, taken May 7, 1943. This is not a teleroentgenogram. The heart is, however, moderately enlarged. B, The heart in Case 2, showing the prominence of the right ventricle. The thickened cusps of the pulmonary valve can be seen and the marked stenosis of the valve is apparent. The pulmonary artery, distal to the valve, is moderately dilated and the wall is delicate and thin.

been able to pass through it. The valve leaflets of the pulmonary artery were distinct and separate, but there was marked stenosis of the annulus, which measured 1 cm. in circumference. The valve leaflets were thickened, and the pulmonary artery in the first portion was thin and somewhat dilated (Fig. 4, B). The aortic valve was normal and measured 2.5 cm. in circumference, and the tricuspid and mitral valves were normal. Each measured 3.5 centimeters. The interventricular septum was intact and the ductus arteriosus was closed. The liver was normal. Sections for microscopic examination of the pulmonary valve were not made.

CASE 3 (G. F., A-303).—A 22-year-old, married woman entered the Massachusetts General Hospital April 20, 1898, complaining of dyspnea and cough of four months' duration, which had become progressively worse for two weeks. She had had two children without difficulty; the younger was 2 years of age. "Heart trouble" had been present for several years, but no history was given of her condition at birth. No history of rheumatic fever was obtained.

The physical examination revealed marked cyanosis of lips, cheeks, ears, and nails, and moderate cyanosis of the skin over the body. The lungs were normal. The heart was enlarged, both to the left and right by percussion, with the left border 1 cm. to the left of the nipple line. No thrill was palpated but a harsh systolic murmur was well heard over the precordial area. In the third and fourth intercostal spaces, to the left of the sternum, the systolic murmur had a higher pitch. The heart sounds at the base were of poor quality and the pulmonary second sound was accentuated. The pulse was regular, with a rate of 90 per minute, and the respiratory rate was 30. The liver extended 5 fingerbreadths below the right costal border and moderate pitting edema was present over the lower extremities. The urine examination demonstrated a small amount of albumin. The edema diminished while on bed rest, and she was discharged, improved, on May 2, 1898.

On June 22, 1898, the patient re-entered the hospital because of increasing edema and dyspnea and right hemiparesis for two weeks. Physical examination was little changed except for a hemiparesis of moderate degree. She was again discharged on July 7, 1898, considerably improved after having received small doses of the tincture of digitalis.

On July 29, 1898, she returned to the hospital because of increasing dyspnea and cyanosis, being unable to lie flat in bed. A sister was said to have died of heart trouble, two weeks before the patient's re-entry. Physical examination revealed intense cyanosis and moderate orthopnea. The lungs were normal. The heart sounds were less loud, and the pulse rapid and regular with a rate of 120 per minute. The right hemiparesis was less marked, and there was little dependent edema. Moderate tenderness was elicited over the liver. The cyanosis increased and, by July 31, the cyanosis was extreme, yet the lungs were negative to examination. Later the same day, she died. A clinical diagnosis was made of chronic endocarditis with mitral regurgitation and, possibly, congenital heart disease.

Autopsy Findings.—Anatomic diagnosis: (1) stenosis of pulmonary valve of heart, congenital; (2) hypertrophy and dilatation of right auricle and ventricle; (3) small, patent foramen ovale; (4) mural thrombosis of right auricular appendage, right ventricle, and left ventricle; and (5) chronic passive congestion of the liver.

No pleural fluid was found, and the lungs were not unusually heavy. The heart weighed 630 grams. The right auricle was unusually large, the cavity being about the size of a lemon. The right ventricle was prominent, and the cavity was large. The right ventricular wall measured 12 mm. in thickness. The cusps of the pulmonary valve were joined to each other and were connected with the wall of the pulmonary valve by three small, smooth bands of tissue; the appearance was produced of four small cusps, each about one-half the size of the aortic cusps. The foramen ovale was open and measured about 5 by 5 millimeters. The left ventricle was slightly dilated, but otherwise was normal. The remaining valves were normal. The interventricular septum was intact. The liver was not remarkable, except for chronic passive congestion.

CASE 4 (E. A. P. E., A5203).—A 43-year-old actress entered the Massachusetts General Hospital July 8, 1927, complaining of progressive weakness and weight loss over a period of ten months. Since early childhood, the patient had had much indigestion, with intermittent episodes of upper abdominal pain, lasting several days and occurring two or three times a year. Her appetite had always been fastidious; she had an aversion to meat and seldom ate red meat but occasionally ate fish. During the ten months preceding entry, she had also noted generalized edema and ascites, with some hyperesthesia of the skin and frequent drenching

night sweats. For the same period of time, she had had four to six small watery stools each day, a sore mouth, and dark, red, circumscribed areas over the dorsum of each hand, varying from week to week. For an indefinite period, some loss of memory and mental confusion had been present. There had been no history of dyspnea, cyanosis, or heart disease.

The physical examination revealed a fairly well-nourished, middle-aged woman with generalized anasarca and cutaneous hyperesthesia. The face was edematous, and the skin and lips were moderately cyanotic. The tongue was red and raw and, over the dorsum of each hand, was a dusky red discoloration with a good deal of crustation. The lungs were normal to auscultation. The heart size was difficult to discern by physical examination. The heart sounds were of good quality and a loud systolic murmur was heard in the second and third intercostal spaces, to the left of the sternum. It was well heard over the posterior chest. A short rough diastolic murmur was also faintly audible at the pulmonic area. The pulmonary second sound was of good quality and equal to the aortic second sound. The blood pressure was not measured because of the edema and hyperesthesia of the skin. The pulse rate on entry was 100 and varied from 90 to 120 during the hospital stay. The abdomen was distended and a large, irregular mass was palpable in the upper abdomen in the region of the liver. The lower extremities were quite edematous and the deep tendon reflexes were hyperactive.

The laboratory data revealed a hemoglobin of 85 per cent; the red blood cell count was 5 million and white blood cell count was 12,000 to 18,000 per cubic millimeter, with a normal differential count. The urine examination was normal. Blood chemical studies revealed the following: nonprotein nitrogen, 42 mg. per cent; sugar, 117 mg. per cent; and total serum protein, 6.1 Gm. per cent. A "portable" chest x-ray film revealed a slight prominence of the pulmonary conus but no appreciable enlargement of the heart. An electrocardiogram demonstrated a sinus tachycardia of 120 per minute, slightly depressed S-T₁ segment, flat T waves in Leads I and II, a low T₂ wave, and a P-R interval of about 0.10 second (Fig. 1, C).

During the first ten days, the patient received 0.2 Gm. of digitalis every day, without any appreciable improvement. A high-vitamin, nutritious diet was likewise given without any striking benefit. She was, at times, confused while in the hospital but, at other times, was very lucid. An abdominal paracentesis on July 21 yielded 2 liters of lemon yellow, cloudy fluid, with a specific gravity of 1.010. The diarrhea continued, her mental confusion increased, and generalized edema became worse. She developed a high fever and died on July 31, 1927. The clinical diagnoses were as follows: (1) pellagra; (2) abdominal neoplasm; (3) slight pulmonic stenosis, probably congenital; and (4) generalized anasarca.

Autopsy Findings.—Anatomic diagnoses: (1) carcinoma of the ileum with metastases to the liver, ovaries, and thoracic duct; (2) pellagra; (3) congenital heart disease, with pulmonary stenosis; (4) chronic passive congestion of the liver; and (5) ascites.

About 500 c.c. of slightly cloudy, blood-tinged fluid were present in each pleural cavity. There was moderate congestion of each lung, particularly in the lower lobes. The heart weighed 260 grams. The right ventricular wall measured 6 mm. in thickness and was definitely hypertrophied. The left ventricular wall measured 1.9 cm. in thickness, and the columnae carneae and the ventricular cavity were normal. The pulmonary valve measured 4.5 cm. in thickness and was moderately stenotic. The valve edges were thicker and more fibrous than normal. The surface of the valve was smooth. The mitral, tricuspid, and aortic valves were normal. There was marked chronic passive congestion of the liver with some atrophy of the liver-cell cords.

CASE 5 (P. S., A-2753).—A 30-year-old salesman entered the Massachusetts General Hospital Dec. 22, 1910, complaining of chills, fever, headache, and cough for four days. The family history was irrelevant. Since infancy he had noted dyspnea on exertion, but this had never been sufficient to confine him to bed. He had also noted a bluish discoloration of the skin at times since infancy, which was especially noticeable whenever he became chilly. At the age of 23 years, the patient had rheumatism. In August, 1910, he was seen in the Medical Outpatient Department where a diagnosis of mitral regurgitation was made. The hands were noted to be cold and blue at this time. During the six months before entry to the hospital, the dyspnea on exertion had increased. He had not been in bed before entry to the hospital.

The physical examination, on entry, revealed a fairly well-developed man who coughed frequently. The extremities and ears were cold and deeply cyanotic. The cyanosis decreased appreciably after he became warmer. There was no clubbing of the fingers or toes. The heart was found to be enlarged, with a diffuse impulse over the precordium, palpable as far as 3 cm. to the left of the nipple line in the fifth intercostal space. The left border of dullness was 2 cm. to the left of the nipple line in the sixth intercostal space. There was a precordial systolic murmur which was best heard in the third and fourth intercostal spaces to the

left of the sternum and was transmitted to the neck, left axilla, and back. The pulmonary second sound was fairly forceful, but indistinct, soft, and rather obscured by the systolic murmur. The aortic second sound was not heard. The systolic blood pressure was 105 mm. Hg, systolic, and the diastolic was indistinct. The pulse was regular and full, with a rate of 100 per minute. The chest examination revealed only a few moist râles at the base of each lung and in the axilla, without bronchial breath sounds. The abdomen was negative.

The laboratory studies demonstrated a hemoglobin of 90 per cent; the white blood cell count was 17,700 and the red blood cell count was 5.8 million per cubic centimeter. The urine contained 3 plus albumin and a moderate number of granular casts. The sputum was like prune juice and contained pneumococci. The temperature was 104° F.

The day after entry, bronchial breath sounds and egophony were noted over the right upper and middle lobes of the lung, with numerous moist râles. The cyanosis increased, and his fever remained at 104° F. He became delirious and died two days after entry. The clinical diagnosis was lobar pneumonia, chronic mitral endocarditis, and a question of congenital heart disease.

Autopsy Findings.—Anatomic diagnoses: (1) lobar pneumonia, right lung; (2) chronic pleuritis, right; (3) stenosis of the pulmonary valve, congenital; (4) fibrous endocarditis of the tricuspid valve, with slight stenosis; (5) hypertrophy and dilatation of the heart; (6) defective closure of the foramen ovale; (7) chronic passive congestion.

The heart weighed 430 grams. The right ventricular wall was greatly thickened and measured 10 to 15 mm. in thickness. The right auricular wall was also thickened and the columnae carneae were markedly thickened. The right auricular cavity was large. The pulmonary valve was about 5.5 mm. in diameter and about 17 mm. in circumference. The orifice of this valve admitted the passage of an ordinary lead pencil. There were three cusps which showed a moderate amount of diffuse fibrous thickening, with fusion of the contiguous cusp margins. The pulmonary artery and its branches were small, but the branches in the lung were of good size. The tricuspid valve measured 10 cm. in circumference, and the leaflets showed a moderate amount of diffuse fibrous thickening which, in places, was quite nodular. The mitral valve circumference was 10 cm., and the cusps were slightly thicker than usual, but the valve was otherwise normal. The foramen ovale presented an oval defective closure about 6 mm. in the greatest diameter. There was moderate chronic passive congestion of the liver.

CASE 6 (L. C., 152471).^{*}—A 5-month-old female infant was brought to the Children's Hospital on Aug. 26, 1931, because of swelling of the right thigh and failure to move it for four days. The infant's mother was said to have had heart trouble since early childhood but had been able to endure two previous pregnancies without appreciable difficulty in labor. The patient had a full-term, normal delivery, and weighed 4 pounds, 11 ounces. A diagnosis of congenital heart disease was made at birth, apparently from the auscultatory cardiac signs. For two weeks before entry to the hospital, the child had been somewhat feverish and, on the day of entry, mild cyanosis about the lips was noted by the mother.

The physical examination revealed an apathetic, acutely ill infant with cyanosis of the face and extremities. The neck veins were not distended. Numerous scattered rhonchi and fine, crepitant râles were heard over both lungs. The heart was thought to be slightly enlarged, and there was a loud, precordial systolic murmur with a palpable thrill. No diastolic murmur was noted. The abdomen was normal, and the right thigh was swollen and held in the flexed position. No clubbing of the extremities was noted. A clinical diagnosis of acute osteomyelitis was made, but the patient was too ill to be subjected to surgery at the time. The temperature ranged from 103.4° to 104.6° F., and the pulse ranged from 120 to 180 per minute.

Laboratory studies revealed a hemoglobin of 65 per cent, a red blood cell count of 4.85 million, and a white blood cell count of 24,400 per cubic millimeter. The urine was normal. Fluid parenterally and supportive measures were of no avail, and the patient died, two days after entry. The clinical diagnoses were: (1) congenital heart disease, (2) osteomyelitis of the right femur, and (3) bronchopneumonia.

Autopsy Findings.—Anatomic diagnoses: (1) septicemia (*Streptococcus hemolyticus*); (2) congenital heart disease with stenosis of the pulmonary valve; (3) acute bacterial endocarditis (pulmonary valve); (4) edema, generalized; (5) acute glomerulonephritis; (6) abscesses of the lungs, myocardium, liver, and kidneys; and (7) osteomyelitis, periostitis, and epiphysitis of the right femur.

^{*}Reported by Farber and Hubbard, 1933.²

The heart was prominent in the region of the right ventricle, and the weight was 30 grams, with an estimated normal weight of 29 grams. The wall of the right ventricle measured 7 mm. in thickness, as compared to that of the left ventricular wall which measured 8 millimeters. The right auricle and right ventricle were slightly dilated. The foramen ovale was closed, and the interventricular septum was intact. The pulmonary ring was markedly stenotic and measured 16 mm. in circumference. The pulmonary cusps were somewhat thickened and the surfaces roughened. The pulmonary artery was of normal size. On the anterior leaflet of the pulmonary valve, attached to the surface next to the pulmonary artery, there was a small, irregular, fresh fibrinous vegetation, 1 by 1.5 by 2 mm., which was firmly attached to the valve surface. No other vegetations were seen and the tricuspid mitral, and aortic valves were normal.

Microscopic examination of the pulmonary valve revealed thickening of the valve, with some increase in connective tissue. In the vegetation attached to the valve, numerous cocci were demonstrable. No scarring was seen in any of the other valves, or in the myocardium.

CASE 7 (H. C., 11901).—A 5-month-old male infant was brought to the Children's Hospital on May 23, 1925, because of constant crying and cyanosis of the skin. For ten days following birth, the patient was said to have been a blue baby. He was noted to be cyanotic following this, but the cyanosis was not very prominent except during crying.

The physical examination revealed a poorly-developed and poorly-nourished male infant, appearing mentally alert. The skin revealed moderate cyanosis, but no clubbing of the extremities was noted. The mucous membranes of the mouth became very cyanotic during crying. The lungs were normal by percussion and auscultation. The heart was thought to be enlarged to the right, and a loud precordial systolic murmur, not rough, was noted; this murmur was transmitted to the left axilla and the left side of the chest posteriorly. The second pulmonic sound was decreased, and a thrill was palpable at the base of the heart in the pulmonic area. The heart rhythm was regular, and the rate was 148 per minute. The abdomen was normal. The extremities were normal, except for the cyanosis. A teleroentgenogram of the chest revealed an enlarged heart shadow, measuring transversely 6.5 cm., but there was no characteristic configuration or abnormality in shape.

The laboratory studies revealed a hemoglobin of 115 per cent, a red blood cell count of 8.75 million, and a white blood cell count of 19,800 per cubic millimeter with 64 per cent lymphocytes, 34 per cent polymorphonuclears, and 2 per cent monocytes. Urinalysis was negative.

There was no change in the course of the disease until June 13, when he developed fever. A blood culture two days later contained a pure culture of streptococci. Signs of sepsis progressed, and he died June 19, 1925.

Autopsy Findings.—Anatomic diagnoses: (1) stenosis of pulmonary valve of the heart, (2) coronary sclerosis, (3) cardiac hypertrophy, (4) chronic passive congestion of the viscera, and (5) bronchopneumonia.

The heart was moderately enlarged and prominent in the region of the right ventricle. The right ventricular wall measured 1 cm. in thickness. The interventricular septum was intact and the foramen ovale was closed. The pulmonary ring was quite markedly stenosed and measured 4 mm. in circumference. There was moderate sclerosis of the coronary arteries. The pulmonary valve was not examined microscopically. The liver showed moderate chronic passive congestion, but there was no evidence of scarring.

CASE 8 (D. L., 134420).—A 15-year-old boy was admitted to the Children's Hospital in April, 1930, because of weight loss of two weeks' duration. In the preceding two years, there had been intermittent edema of the genitalia and extremities and marked mottling of the skin on exposure to the cold.

The physical examination revealed an emaciated boy with a barrel-shaped chest and a marked depression of the sternum. There was moderate scoliosis of the dorsal spine. Evidence of fluid was found in the left side of the chest. The heart sounds were of good quality, and both systolic and diastolic murmurs were described over the precordium. The spleen was enlarged, and pitting edema of the lower extremities was quite marked.

The laboratory studies revealed a normal urine, except for a Grade 1 albuminuria. The hemoglobin was 128 per cent (Sahli); the red blood cell count was 6,230,000 and the white blood cell count was 9,050 per cubic millimeter, with a normal differential count. There was no fever. The x-ray films of the chest revealed evidence of a considerable amount of fluid in the left lower lateral chest. The heart was markedly enlarged and displaced to the right.

A rather "flocculent" congestion or edema of the lungs was described. Thirty cubic centimeters of bright, sanguineous fluid was removed from the left side of the chest by thoracentesis. It was thought at the time that the pleural fluid on the left was due to congestive heart failure.

On March 8, 1937, he was readmitted to the hospital. At this time there was observed little physical development over that of his previous entry. Six months before re-entry, he had had his appendix removed under local anesthesia at another hospital. His complaints on the later entry were dyspnea and edema of the legs. A large amount of fluid was removed from the left side of the chest, on entry, a culture from which revealed *Staphylococcus aureus*. On March 14, 1937, the heart was found to be enlarged, and both systolic and diastolic murmurs were described, indistinct at the apex, and loudest in the hollow of the deformity of the chest. A thrill was palpated over the lower end of the sternum, and the pulmonary second sound equaled the aortic second sound in intensity, although it was not accentuated. The liver was moderately enlarged. The fingers were long, but there was no clubbing.

The hemoglobin, on this entry, was 90 per cent; the red blood cell count was 4,900,000 and the white blood cell count was 22,100 per cubic millimeter.



Fig. 5.—The heart in Case 8. A, The right ventricle is open to demonstrate the moderate stenosis and scarring of the pulmonary valve and ring. The scarred tricuspid valve with the thickened chordae tendineae can be seen. The hypertrophy of the wall of the right ventricle is also apparent. B, The left ventricle and auricle are open to demonstrate the abnormal mitral valve, with thickening and shortening of the chordae tendineae. The fenestration of the septum secundum is also apparent.

He was then discharged home, where he carried out simple activities but was bothered by orthopnea and an occasional slight rise in temperature. He was re-admitted to the hospital on March 30, 1937, where a rib resection was carried out two days later. Following this operation his temperature remained elevated, the pulse became fast, and he died on April 6, 1937.

Autopsy Findings.—Anatomic diagnoses: (1) bacteriemia, *Str. hemolyticus*; (2) congenital heart disease with: (a) stenosis of the pulmonary valve, (b) absence of one coronary artery, (c) fenestration of the aortic valve leaflets and septum secundum, (d) hypertrophy of the right ventricle, (e) network of Chiari, and (f) scarring of the tricuspid, aortic, and mitral valves; (3) bronchopneumonia; (4) chronic pleuritis and empyema, left, old; (5) focal necrosis of the liver with bile stasis and periportal cirrhosis; (6) chronic passive congestion, generalized; and (7) pulmonary edema.

The heart was moderately enlarged, and the right ventricle was hypertrophied. The foramen ovale was closed, and the interventricular septum was intact. The pulmonary valve was moderately stenosed and measured 2.5 cm. in circumference, as compared with 3.5 cm. for the aortic valve circumference (see Fig. 5). The valve leaflets were thickened and firm. The individual leaflets were long, with deep cryptlike sinuses behind each one. The tricuspid valve was thickened, and the chordae tendineae were thickened and measured 1.2 cm. in length. The mitral valve was similarly affected (Fig. 5, B), but there was no stenosis of the valve. There was thickening of the leaflets of the aortic valve, but no stenosis was produced. Several small fenestrations, measuring 1 to 3 mm., were present in the anterior and posterior leaflets of the aortic valve and in the septum secundum (Fig. 5, B).

Microscopic examination of sections, taken from the pulmonary valve annulus, revealed abundant, highly collagenous connective tissue. Slight vascularization of this tissue was present, and an occasional vessel was surrounded by lymphocytes. The portal veins and sinusoids of the liver were congested, and there was quite a marked increase in the periportal connective tissue. Strands of connective tissue extended from one portal area to another. Moderate infiltration of this tissue with lymphocytes, monocytes, and a few polymorphonuclear leucocytes was present.

CASE 9 (B. C. H., 1014034).^{*}—A 20-year-old white girl was first admitted to the Boston City Hospital in March, 1937, with a complaint of dyspnea on exertion of one year's duration. She had not been a "blue baby" and had no history of rheumatic fever or joint pains.

The patient was well nourished and moderately well developed. There was visible pulsation of the cervical veins. The heart was enlarged to the right and left, and the point of maximal impulse was in the fifth intercostal space, 10 cm. from the midsternal line. The right border of cardiac dullness was 4 cm. from the midsternal line in the fourth intercostal space. There was a precordial bulge, with a palpable systolic thrill felt along the left border of the sternum. There was a harsh, high-pitched systolic murmur with the point of maximum intensity at the second intercostal space, to the right of the sternum. It was transmitted widely, over the precordium, and upward, along the left side of the neck, and, slightly, along the right side of the neck. There was also a systolic "shock," palpable over the precordium. A loud systolic murmur was heard over the spine and upper chest posteriorly. The blood pressure measured 114/82, and the lungs were clear to examination. The abdomen was normal. There was moderate pretibial and ankle edema.

During her hospital stay, the laboratory data were as follows: hemoglobin, 82 per cent; red blood cell count, 3.75 million, and white blood cell count, 9,600 per cubic millimeter; sedimentation rate, 5 mm. per hour; blood Hinton test, negative; and urine normal, with a specific gravity of 1.020. No growth was obtained from two blood cultures. A teleroentgenogram of the chest was interpreted as showing cardiac enlargement with a marked "rheumatic" deformity. The pulsations were poor during fluoroscopy. Electrocardiogram showed a normal sinus rhythm and a high degree of right axis deviation. The S-T segments were depressed in Leads II and III, and the T waves in the same leads were inverted (see Fig. 1, D and E).

She was placed on bed rest, and fluids were restricted while in the hospital; the edema subsided rapidly. She was discharged after two weeks, considerably improved.

The patient next returned to the hospital in December, 1938, eighteen months later. Six weeks before this admission, she had first noticed swelling of the abdomen followed by edema of the ankles. In addition, she had had gradually increasing dyspnea on exertion.

When examined she appeared well nourished with slight orthopnea, but without cyanosis. The neck veins were distended. Over the left lower chest posteriorly, there was dullness to percussion, diminished voice and breath sounds, and a few, medium, coarse moist râles. The heart findings were essentially the same as on the previous entry. Shifting dullness and a fluid wave were demonstrated in the abdomen. The liver and spleen were not felt. There was moderate pitting edema over the sacrum and ankles.

The venous pressure in the arms was 30 cm. of water and that in the legs, 31 cm. of water. The electrocardiogram had not changed appreciably. The x-ray heart shadow was described as globular in shape and some increased density was noted in the left lower chest, which was thought to be due to fluid. By fluoroscopic examination, marked symmetrical enlargement of the heart was noted. The cardiac pulsation in the region of the left ventricle was diminished to absent, while the pulsation in the region of the right ventricle was described as slight.

^{*}Case 1 of Wexler and Ellis, 1944.

The patient was treated with digitalis, Salyrgan, restriction of fluids, and rest in bed. The edema and ascites gradually disappeared, and she became less dyspneic, but the neck veins remained distended. The cardiac shadow did not change in size or contour during this time. She was discharged on the twenty-fourth day of her hospital stay with instructions to continue taking digitalis and gradually to resume moderate activity.

The patient again entered the hospital in October, 1940, because of increasing swelling of her abdomen and dyspnea. She had been taking 0.1 Gm. of digitalis daily, since her previous discharge and had restricted her physical activity. If the patient remained in bed, the size of her abdomen decreased; if she attempted to resume any activity, the ascites would sometimes return. The patient had not noted cyanosis, and her ankles had not been swollen.

The blood pressure was 110/72; the pulse rate was 92 per minute; the respiratory rate was 24; and the temperature was 98.6° F. The heart signs and sounds were essentially the same as during the previous admission. There were ascites and sacral edema but no ankle edema.

The laboratory studies revealed a hemoglobin of 85 per cent, a red blood cell count of 4.15 million, and a white blood cell count of 6,700 per cubic millimeter. The total protein varied between 5.3 and 5.7 Gm. per cent. The urine contained albumin, 1 to 3 plus, and many white blood cells in clumps. The venous pressure in the arms was 31 cm. of water on admission, and it gradually dropped to 19 cm., on discharge. The circulation time, by the sodium cyanide method, was 50 seconds, on admission, and 30 seconds, on discharge. Electrocardiograms and teleroentgenograms of the chest showed no significant changes from those of the previous entry. The basal metabolic rate was -2. While in the hospital she received 0.1 Gm. of digitalis every day, mercupurin, 2 c.c. every other day, and rest in bed. She repeatedly had reactions to mercupurin, which consisted of a feeling of faintness, transient dyspnea, and a feeling of impending disaster for a few minutes after the injection, which was always given slowly. On this regime she improved, although the ascites never completely subsided. She was discharged after fifty-two days.

In May, 1941, the patient had her final hospital admission because of dyspnea and abdominal swelling. Physical examination showed a thin girl with evidence of moderate loss of muscular substance, particularly over the upper part of her body. The heart findings were much the same as before, and she also had signs of fluid in both pleural cavities. Her abdomen was greatly distended with fluid.

The laboratory and clinical data were much the same as before, including the venous pressure values and circulation time. In addition, the total serum protein was 4.8 Gm. per cent: the globulin was 2.4 Gm. per cent, and the albumin was 2.4 Gm. per cent. Urobilinogen determinations in the urine varied between 1:1 and 1:8, the hippuric acid excretion was 1 Gm. in four hours, and the prothrombin time was 36 per cent of normal. The bromsulfalein test showed 90 per cent retention in five minutes, 45 per cent retention in 15 minutes, and 20 per cent retention in 30 minutes.

She was placed on bed rest and given digitalis and Mercupurin. In the middle of the second hospital month, auricular fibrillation appeared for the first time (Fig. 1, E) and was present thereafter. The ascites and pleural fluid persisted and at the end of the third month, a right thoracentesis was performed with recovery of clear yellow fluid. Culture of this fluid yielded no growth. One week later, 12 liters of a similar clear transudate fluid were removed slowly by abdominal paracentesis; this fluid was likewise sterile to culture. There were an estimated 6 liters left in the abdominal cavity. Fluid slowly reaccumulated in the right side of the chest and abdomen. The right side of the chest was again tapped, a few days later, and 1,200 c.c. of clear fluid were removed without incident. About two hours later, Mercupurin was given intravenously, as had been done on many previous occasions, and, directly after the injection, the patient's breathing became rapid and shallow. After a few seconds she developed acute opisthotonus, the heart stopped beating, and she expired.

Autopsy Findings.—Anatomic diagnoses: (1) pulmonary stenosis, congenital, with marked hypertrophy of the right auricle and ventricle; (2) mural thrombus, right auricle; (3) cirrhosis of the liver; (4) ascites and hydrothorax, right; (5) chronic passive congestion of viscera; (6) fibrocaseous pulmonary tuberculosis, involving the right apex, diaphragmatic pleura and tracheobronchial lymph nodes; (7) hyperplasia of red cell series of bone marrow; and (8) healed perisplenitis.

The body was that of an underdeveloped, poorly nourished white girl. There was no peripheral edema. Five liters of clear yellow fluid were present in the peritoneal cavity and 300 c.c. of similar fluid were found in the pericardial cavity. Two liters of blood-tinged fluid were present in the right pleural cavity, and the pleural surfaces were coated with a thin film of friable, gray-green purulent material. This was most marked over the surface of the

diaphragm. The heart weighed 380 grams. The edges of the cusps of the pulmonary valve were fused so that the valve opening measured but 0.5 cm. in diameter. The valve edges were slightly thickened but were smooth and showed no evidence of calcification or of inflammation (Fig. 6). The bodies, bases, and commissures of the valve were not remarkable. The pulmonary ring at the base of the valve measured 5 cm. in circumference. Microscopic sections, taken from the base of a pulmonary valve cusp, showed no abnormalities. The right ventricle was hypertrophied, so that the wall measured 1.8 cm. in thickness. The papillary muscles were somewhat flattened and the ventricle appeared dilated. The right auricle was markedly dilated and, attached to the wall of the right auricular appendage, was a soft gray-red thrombus. The wall of the left ventricle measured 1 cm. in thickness, and the chamber was not remarkable. The left auricle was not enlarged. The tricuspid, mitral, and aortic valves and the coronary vessels were negative. The right lung weighed 200 grams. There was a

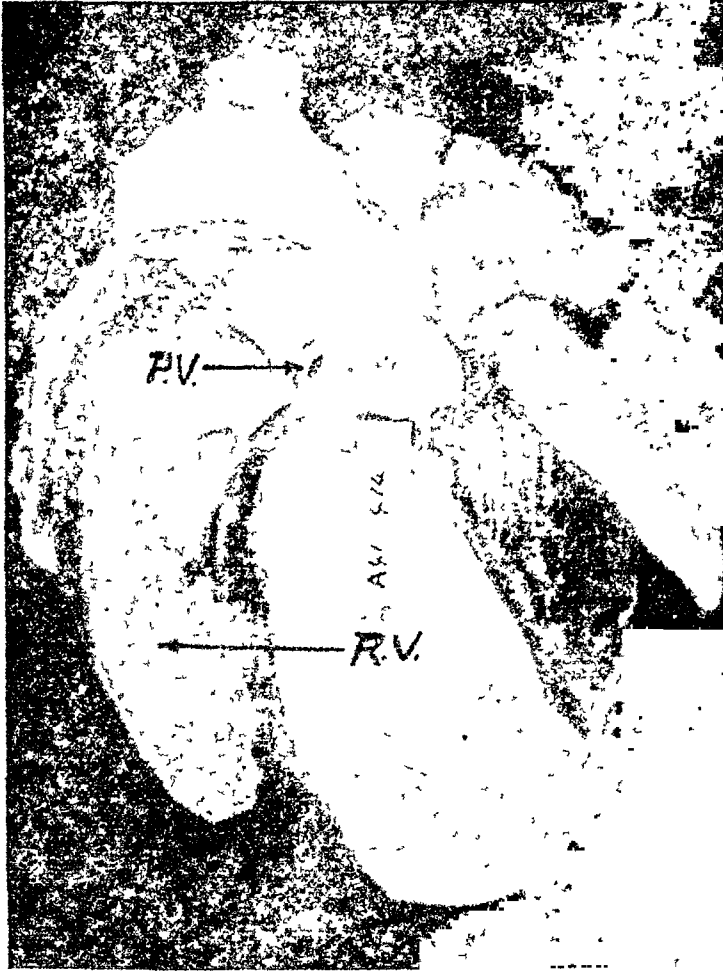


Fig. 6—The heart in Case 9, with the right ventricle open. The marked hypertrophy of the right ventricular wall (R.V.) is apparent. The pulmonary valve leaflets were fused together forming a dome at the top of which was the small aperture (P.V.) The pulmonary annulus was not particularly stenosed.

firm, gray nodule 0.3 cm. in diameter at its apex, which, on histologic examination, showed typical fibrocaseous tuberculosis. The tracheobronchial lymph nodes were moderately enlarged and contained caseous nodules, which were also demonstrated by histologic sections to be due to tuberculosis. The left lung weighed 120 grams and was negative upon examination. The liver weighed, 1,090 grams. The surface was red brown in color and coarsely and irregularly nodular. The parenchyma was divided into rough, irregular nodules by bands of firm, gray-white fibrous tissue. Microscopic examination showed extensive replacement of liver cells by broad bands of scar tissue. There was marked congestion about the central veins, and the liver cells around many of these veins were replaced by fibrous tissue. The spleen weighed 160 grams and was firm in consistency. The combined weight of the kidneys was 250 grams. No abnormal changes were found on gross and microscopic examinations. The bone marrow showed moderate hyperplasia of blood cells of the erythrocytic series.

CASE 10 (A. W., A09-107).—A 34-year-old housewife entered the Boston City Hospital in May, 1906, because of dyspnea, abdominal swelling, and edema of the lower extremities of three months' duration.

At the time of admission, the temperature was 98° F.; the pulse rate was 100 to 140 per minute; and the respirations were 25 to 40. The patient was well nourished and of normal development. Edema was described as generalized, and the patient suffered from dyspnea and orthopnea. There was moderate exophthalmos. The neck veins were slightly distended. The heart was percussed 4.5 cm. to the right of the sternum. The upper and left cardiac borders could not be identified. The apex beat was felt in the sixth intercostal space, slightly to the left of the midclavicular line. The heart action was irregular in force and rhythm. The first heart sound was sharp and was preceded at the apex by a presystolic "roll." There was a ringing second sound at the base, just to the left of the sternum. A presystolic thrill was felt at the apex, and a systolic thrill was present at the base and, at times, over the entire precordium. There was a loud systolic murmur heard at the base of the heart and this was most marked just to the left of the midsternum. There were a systolic murmur and a diastolic bruit at a point slightly below the middle third of the left clavicle. A to-and-fro pericardial friction rub was heard at the apex and, at times, over the midprecordium. The radial pulses were small and irregular in force and rhythm. The cardiohepatic angle was normal. There was slight dullness to percussion over the posterior portion of the right lower lung, and moist râles were heard by auscultation of the right base. Anteriorly, the entire left lung was flat by percussion, and there was distal bronchial breathing and absent tactile fremitus. The posterior portion of the left lung was dull by percussion over the upper half; the lower half was flat by percussion, and the breath sounds were diminished. An occasional moist râle was present at the left lung base. The abdomen was distended and tense. The abdominal wall was edematous. The flanks were flat, when percussed, and a fluid wave and shifting dullness were demonstrated. The liver was palpated 4 fingerbreadths below the right costal margin. There was marked edema of the legs. Several superficial excoriations and ulcerations were present on the right lower leg. There was a papillary eruption about the elbows and on the back. The knee jerks were not obtained.

Urinalysis revealed a specific gravity of 1.012, a slight amount of albumin, and numerous hyaline and granular casts.

The patient was given digitalis. On the second hospital day approximately 2,000 c.c. of fluid were removed from the left side of the chest. The patient's condition improved for a few days but then became progressively worse; she died on the twelfth hospital day.

Autopsy Findings.—Anatomic diagnoses: (1) pulmonary stenosis, congenital, with marked hypertrophy of the right auricle and ventricle; (2) mural thrombus (right auricle) ball thrombi, (left ventricle) obliterative pericarditis; (4) congestive cirrhosis of the liver; (5) ascites (bilateral hydrothorax); (6) atelectasis (left lung); (7) infarct of the right kidney; and (8) leiomyomata of the uterus.

There was marked edema of the lower extremities and moderate edema of the chest wall and face. There were numerous sharply demarcated, circumscribed ulcers over the lower extremities. The peritoneal cavity contained approximately 3 liters of clear serous fluid. One liter of similar fluid was present in the left pleural cavity, while 500 c.c. of fluid were present in the right pleural cavity. The pericardial cavity was obliterated by dense inelastic adhesions, except over the right auricle. The heart weighed 520 grams. The edges of the cusps of the pulmonary valve were interadherent for approximately one-third of their total length, with consequent narrowing of the functional opening to 1 cm. in diameter. The valve cusps were not thickened and the valve sinuses were deep. There were a few small areas on the free margin of the tricuspid valve which were thickened. The leaflets of the mitral valve were slightly thickened, along their line of closure, and along their free margins. The aortic valve was normal. The right auricle was approximately three times the usual size and was markedly dilated. In the auricular appendage was a large, firmly adherent mass of mottled red and gray clot. The right ventricle was hypertrophied; its wall measured 1.5 cm. in thickness, and the papillary muscles were larger than those of the left ventricle. The left auricle was not remarkable. The wall of the left ventricle was thickened and measured 1.75 cm. in width. Two red and white, laminated ovoid masses, with uniformly smooth surfaces, were lying free in the cavity of the left ventricle. These measured 2 by 1 by 1 and 1 by 1 by 0.5 centimeters. Throughout the ventricular muscle of both cavities were areas of pale yellow and dark red mottling and, in many places, opaque, white, irregular areas. The coronary sinus was dilated so that the forefinger could be passed readily through the first few centimeters of its length. The coronary arteries were not remarkable. Microscopic sections showed focal areas of replacement of the myocardium by scar tissue. The liver weighed 1,500 grams.

The surface was nodular, but soft, and could be cut without undue resistance. The parenchyma was mottled with large, irregular areas of dark red and bright yellow. No lobular markings could be distinguished. The hepatic veins were greatly dilated.

Microscopic sections of the liver showed a marked increase in connective tissue. This tissue was arranged, in some areas, in the form of dense circumscribed bands and, in other areas, as irregularly branching, dense masses. These masses contained isolated groups of liver cells, bile ducts, and blood vessels. The liver sinusoids were considerably dilated and many of the liver cell columns were shrunken.

CASE 11 (W. J. H.).—An 11-year-old boy entered the Boston City Hospital on April 10, 1910, complaining of headache and eye trouble of one week's duration. The headache had become progressively worse. Apparently, also for the first time, he had noted mild dyspnea on exertion and cyanosis during the one week before entry. For two days there had been moderate drowsiness. The family and past histories were irrelevant.

The physical examination revealed a semistuporous boy who was irritable when disturbed. There was paresis of the muscles of the right side of the face and ptosis of the left eyelid. The lungs were clear to examination. The examination of the heart revealed a rough systolic murmur, heard all over the precordium, but it was loudest at the base, where there was an associated thrill. There was no paralysis of the extremities. The temperature was 99° F. The pulse rate ranged from 60 to 90 per minute, and the respirations were 20 per minute. When a lumbar puncture was done, clear fluid was obtained. Two days after entry the patient suddenly became cyanotic; the respirations became gasping in character and then ceased. The heart action continued for a short time after respiratory movement had stopped. The clinical diagnoses of brain abscess and pulmonary stenosis were made.

Autopsy Findings.—Anatomic diagnoses: (1) cerebral abscess; (2) pulmonary stenosis, congenital; (3) hypertrophy of the right ventricle; (4) chronic passive congestion of the liver and kidneys; and (5) patent foramen ovale.

The heart was enlarged, weighing 340 grams; there was particular prominence of the right ventricle. The left auricle and ventricle were normal. The pulmonary valve ring measured 4 cm. in circumference while the aortic valve measured 5 centimeters. The pulmonary cusps were uniformly about 1 mm. thick and presented unusual stiffness, with slight irregularity. No calcification was found. The cusps were fused along the edges so that the outlines were nearly obliterated and a buttonhole orifice, 9 mm. long was produced. The tricuspid, mitral, and aortic valves were normal. The foramen ovale was patent and measured 1.1 by 0.3 centimeters. The wall of the right ventricle was markedly thickened and measured 2.5 cm. across, while the wall of the left ventricle was the usual size and measured 1 centimeter. The interventricular septum was intact. The lungs and liver were normal except for moderate congestion. In the left temporo-occipital lobe of the brain there was an abscess measuring 4.5 cm. in diameter, which contained foul-smelling pus. Microscopic examination of sections of the myocardium were negative.

DISCUSSION AND COMMENTS

It is apparent in reviewing the cases (Table I) that, although the degree of pulmonary stenosis varied somewhat, there was moderate to marked stenosis of the pulmonary valve, or pulmonary annulus, in all except Case 4. It is also apparent that the degree of right ventricular hypertrophy was a good index as to the degree of stenosis. There seemed to be two types of stenosis, one of which affected, primarily, the pulmonary annulus with marked scarring of the annulus and the valve leaflets. This type of stenosis predominated in nine cases. The other type was the result of fusion of the edges of the valve leaflets to form a dome, with an aperture at the peak of the dome. This was present in two cases and was best exemplified in Case 9. Similar cases have been reported.^{5, 6} The right auricle was not infrequently dilated and, in three cases, mural thrombi were found therein. No patient was observed, however, to have suffered from pulmonary embolism or infarction.

The age incidence varied from infancy (three cases) to 43 years, although in the latter case there was only a mild degree of pulmonary stenosis. Two patients lived to the fourth decade with quite a high degree of pulmonary stenosis.

TABLE I

CASES	AGE (YRS.)	SEX	DYS-PNEA	SYSTOLIC MURMUR	CYANOSIS	PATENT FORAMEN OVALE	DEGREE OF PUL- MONARY STENOSIS	RIGHT VENTRIC- ULAR HYPER- TROPHY	DILATED PUL- MONARY ARTERY	CAUSE OF DEATH	REMARKS
1	18	M	+++	+++	+++	++	+++	+++	+	Heart failure	Talipes varus
2	4.5 months	F	0	+++	0	+	+++	+++	+	Subdural hematoma	Right auricular and ventricular thrombi, large right auricle
3	22	F	+++	+++	+++	++	+++	+++	0	Heart failure	
4	43	F	0	++	+	0	+	+	0	Carcinoma, pellagra	
5	30	M	++	+++	++	+	+++	+++	0	Pneumonia	
6	5 months	F	0	+++	+	0	+++	+++	0	Osteomyelitis, septicemia	
7	5 months	M	0	+++	++	0	+++	+++	0	Septicemia	
8	16	M	++	++	+	0	+++	+++	0	Heart failure, septicemia	Depressed sternum, hepatic cir- rhosis
9	24	F	+++	+++	0	0	+++	+++	0	Heart failure, mercurial reac- tion	Hepatic cirrhosis
10	34	F	+++	+++	0	0	+++	+++	0	Heart failure	Right auricular thrombi, hepatic cirrhosis
11	11	M	+	+++	+	++	++	++	0	Cerebral abscess	

There was no definite preponderance of either sex, the females numbered six and the males, five.

A systolic murmur was present in each case and there was a high correlation between the intensity of the murmur and the degree of stenosis. The intensity of the murmur was usually described as maximal at the base of the heart, along the left sternal border in the second and third intercostal spaces. It was also well heard, generally, over the precordium. The intensity of the murmur, together with the lack of change of the character of the murmur with change in position and respiration, enabled one to differentiate it from the common physiologic pulmonary systolic murmur. The transmission of the murmur was likewise important. The murmur was well heard in the cervical region, particularly on the left side, and was well transmitted to the posterior portion of the chest and usually maximally in the left lower scapular region. This transmission of the murmur would tend to differentiate it from the murmur of a patient with an interventricular septal defect. In the latter case, the murmur is transmitted much less well upwards, or to the posterior chest wall. An interauricular septal defect was considered in the differential diagnosis of the murmur in a few cases but the intensity of the murmur was considerably greater in the cases of pulmonary stenosis than one would expect in cases with an interauricular septal defect. A thrill was frequently noted in the pulmonic area and was more frequent in the cases with the more intense murmurs. In two cases (Cases 4 and 8) diastolic murmurs were described in the pulmonic area, which indicated some regurgitation through the deformed pulmonary valve. The apical diastolic murmur described in Case 10 is difficult to reconcile with the anatomic findings. It is possible that ventricular dilatation, as in acute or subacute rheumatic myocardial involvement without mitral stenosis, might have caused it. The second heart sound in the pulmonic area was heard in all the cases, but was described as being diminished in intensity in four cases. It is difficult to appreciate how the second heart sound could have had its origin in the pulmonary valve in some cases of marked scarring of the annulus. This raises the question as to whether the second sound heard in the pulmonic area may not have, in part at least, been transmitted from the aortic valve. This, in fact, is quite probable. In two cases the second pulmonic sound was described as accentuated.

Cyanosis was of a significant degree in four cases, while in the remaining cases it was negligible. Cyanosis was more common, and of a higher degree, in the patients with patency of the foramen ovale. Of the 11 patients, five had a variable degree of patency of the foramen ovale. In Case 1, the patient probably had the most pronounced cyanosis, which was not of a high degree, however, until the last six years of his life. It was during this time that the pressure on the right side of the heart doubtless increased and resulted in a flow of blood from the right auricle to the left auricle, mixing venous blood with arterial blood. The relatively late onset of cyanosis, which progresses, has been noted previously in cases with pulmonary stenosis.⁷

Congestive heart failure was the chief or contributing cause of death in only five of the cases presented here. The three infants all died of causes other than heart failure, although one patient showed evidence of early acute bacterial endocarditis (Case 6). This suggests that pulmonary stenosis is usually compatible with life until the third or fourth decade, when congestive heart failure becomes severe. The patients with the congestive heart failure were also the patients with significant dyspnea. Pleural effusion was found in only two cases. The circulation time was measured in one case and was considerably prolonged,

which indicated that the circulation from the arm into the pulmonary artery was slow, since there was little pulmonary congestion to slow the circulation through the lung.

One patient had minimal pulmonary tuberculosis. We were thus unable to confirm, in this series, the high incidence of pulmonary tuberculosis that has been reported to be associated with pulmonary stenosis.⁸

The electrocardiograms which were taken in four cases showed a high degree of right axis deviation in the three cases in which there was marked hypertrophy of the right ventricle; in the fourth patient, with less pulmonic stenosis, the situation was complicated by avitaminosis. The degree of right axis deviation was similar to that seen in cases with the tetralogy of Fallot and served to differentiate these cases from those with an isolated patency of the interventricular septum in which the electrical axis is generally normal. In the fourth case the electrical axis was normal and there was only slight hypertrophy of the right ventricle. The intraventricular conduction was normal, although right bundle branch block has been noted in pulmonary stenosis.⁶

There was no characteristic configuration of the heart by x-ray examination in the several patients who were studied by fluoroscopy and roentgenography. The heart was generally enlarged in all the patients studied, and in Case 1 there was significant dilatation of the pulmonary artery. This was, perhaps, a result of the presence of a patent foramen ovale. Dilatation of the pulmonary artery was noted in one other case in which there was likewise a patent foramen ovale. In at least two of the sixteen patients studied by Abbott in which pulmonary stenosis was complicated by patency of the foramen ovale, dilatation of the pulmonary artery was noted. Dilatation of the pulmonary artery is common, of course, in patients with isolated interauricular septal defects but in such cases, in contrast to these herewith presented, there is a clear cause, namely, the overloading of the pulmonary circulation. Pulmonary regurgitation, obviously present in a few of these cases of pulmonary stenosis, and quite possibly not demonstrable clinically in others, may be a factor.

The controversial concept of fetal endocarditis has been recently reviewed by Gross.⁹ The accumulating evidence from case reports,¹⁰ and from critical analysis, casts considerable doubt as to whether such a disease exists. To our knowledge, no observations of the acute inflammatory disease have been reported, and the etiological agent is hypothetical. A more likely concept is that of a developmental defect, since convincing evidence of inflammation is not present. This may be, as Gross suggests, a result of arrest or closure of arteries, resulting in bland infarcts and fibrosis. In the several heart valves of this series which were examined microscopically there was moderate fibrosis, but no other convincing stigmas of a previous infectious disease. Another point in favor of anomalous or defective development is the presence of other developmental defects in the heart or elsewhere in the body. In two cases of the present series there was another congenital anomaly present (Cases 2 and 8). Five patients (Table I) had patency of the foramen ovale, and one patient (Case 8) had fenestration of the septum secundum, absence of one coronary artery, and scarring of the other three valves of the heart. The fusion of the cusp edges, with the formation of a dome with a central aperture, in Case 9, was unusual and is similar to other cases reported.^{5, 6}

The recent observation¹¹ of the association of congenital cataracts and congenital heart disease in children whose mothers contracted rubella in the first two months of pregnancy is of interest in relation to congenital heart disease. The reports do not specify the type of congenital heart disease present, and this

question will have to await further elucidation. The observations give considerable support to the view that some types of congenital heart disease may result from an exanthematous disease occurring in the mother and affecting the fetus during the early months of pregnancy. The histories of the mothers of the patients presented in this series of cases are lacking in specific evidence for such an infection, although such may have been present in some. The importance of questioning the mothers of patients with congenital heart disease, regarding the occurrence of exanthemata during pregnancy, is evident.

Sufficient scarring of the liver was present in three cases to warrant a diagnosis of hepatic cirrhosis. In Case 9 the scarring was marked. Since only five of the patients in this series had heart failure, the presence of three cases of congestive hepatic cirrhosis is significant. Pulmonary stenosis with chronic heart failure, then, may be considered, along with chronic constrictive pericarditis, to be associated with a relatively high incidence of congestive cirrhosis of the liver.¹²

SUMMARY

1. Eleven cases are reported herein of stenosis of the pulmonary valve in which the interventricular septum has been intact. In five of the patients there was associated patency of the foramen ovale of variable size. In ten of the cases the pulmonary stenosis was of sufficient degree to result in moderate to marked hypertrophy of the right ventricle.

2. Electrocardiographic and roentgenographic data are presented and discussed. A high degree of right axis deviation in the electrocardiogram is characteristic.

3. Heart failure was the cause of death in five of the patients, while causes unrelated to the heart accounted for the other deaths, including that of the three infants. Hepatic cirrhosis was observed in three of the five patients dying of heart failure.

4. The etiology of pulmonary stenosis and congenital heart disease is discussed.

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A NOTE ON THE SEROLOGIC CLASSIFICATION OF STREPTOCOCCI ISOLATED FROM SUBACUTE BACTERIAL ENDOCARDITIS

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SINCE its introduction by Thiercelin¹ the term "enterococcus" has been variously applied as a synonym for *Streptococcus fecalis* and as a loose term including all fecal streptococci which exhibit one or more of the characteristics usually attributed to this group of microorganisms. Andrews and Horder² pointed out that such streptococci are isolated occasionally from cases of subacute bacterial endocarditis and other human infections. More recently, with respect to the streptococci isolated from subacute endocarditis, the classifications most frequently encountered in the literature are "alpha" or simply "green-producing" streptococci. Bacterial endocarditis due to the "enterococci" has been recorded in a few instances; Skinner and Edwards,³ in a recent survey of the literature, cited thirty-seven cases, and Moran⁴ reported twenty cases in which the streptococci isolated were probably "enterococci."

The bacteriologic methods employed in the identification of "alpha" or "green-producing" streptococci usually indicate nothing as to the exact identity of the strain. The classification, "enterococci," as pointed out by Sherman,⁵ also is based on biologic features which are characteristic of, but not limited to, the group of organisms in question. Lancefield⁶ and Sherman⁵ reported that those organisms previously classified as "enterococci," despite marked biochemical differences, contain a common group antigen which places them in Group D (Lancefield). It has been observed over a period of years in this laboratory that strains which would have been classified as *Str. viridans* by methods other than group precipitation tests frequently belong to Lancefield Group D.

Since many of the cases of endocarditis reported as due to "alpha" streptococci or "enterococci" were studied before the development of group precipitation techniques, there are few data available on the serologic classification of streptococci isolated from the blood cultures and other sources on cases of subacute bacterial endocarditis. Skinner and Edwards³ cited one case in which the streptococci isolated were shown to belong to Group D and added two more from their own observation. More recently, Rantz and Kirby⁷ described three cases as being due to Group D streptococci, and Wheeler and Foley⁸ added four more cases.

During the past two years, the streptococci isolated from seventeen additional cases, diagnosed as subacute bacterial endocarditis in various local hospitals, have been studied in this laboratory. In addition to the serologic classification of the strains isolated from these cases, the reaction on blood agar was

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determined on Huntoon's unenriched hormone agar,⁹ containing 5 per cent sterile, defibrinated horse blood incubated aerobically, anaerobically, and under partial carbon dioxide tension (10 per cent) at 37° C. for forty-eight hours. In general, no consistent qualitative differences in blood agar reaction on media incubated in the various atmospheres were noted. Since the blood agar reaction depends on so many factors other than the biology of the cell and is relatively inconsistent and unstable for many non-Group A streptococci,^{10, 11} each strain was tested for the production of soluble hemolysin.¹² A volume of 0.5 ml. of a ten to sixteen-hour culture in streptococcus toxin broth¹³ was combined with 0.5 ml. of a 5 per cent suspension of defibrinated, washed rabbit erythrocytes and incubated in a water bath at 37° C. for two hours, centrifuged, and examined for evidence of hemolysis. Rabbit erythrocytes and saline and controls with known hemolytic and nonhemolytic streptococci (Lancefield strains J/17/A-4 and O/90-R, respectively) were included. None of the test strains produced soluble hemolysin.

All strains were tested for heat resistance.⁵ Samples of 1 ml. of ten to sixteen-hour broth cultures were incubated in a water bath at 62° to 63° C. for one-half hour, allowed to cool, then streaked on 5 per cent horse blood agar and incubated aerobically at 37° C. for forty-eight hours.

The results of these tests are summarized in Table I, together with the serologic classification of these strains, as well as the four previously reported by Wheeler and Foley.⁸ Four distinct serologic types have been recognized within the Lancefield Group D in this laboratory.¹¹ Since there seemed to be no correlation between serologic type and biochemical activity, various other biochemical tests which were done have been omitted from Table I.

As pointed out by Lancefield,¹⁰ hemolytic activity is not as closely correlated with the serologic group as was first supposed. The existence of nonbeta strains, serologically identical with beta strains within a given serologic group, is well illustrated in the small series recorded in Table I. The ability to withstand high temperatures, long considered characteristic of the "enterococci,"¹⁴ is not a sufficient differential criterion, as indicated in Table I, when the "enterococci" are considered as a serologic group.

From these data it would appear that strains which are assigned such classifications as "alpha" or "green-producing" streptococci, when isolated

TABLE I. SEROLOGIC CLASSIFICATION OF STREPTOCOCCI ISOLATED FROM TWENTY-ONE CASES DIAGNOSED AS SUBACUTE BACTERIAL ENDOCARDITIS

AGE OF PATIENTS	SOURCE OF CULTURE	NUMBER OF CASES	REACTION ON 5% HORSE BLOOD AGAR	HEAT RESISTANCE	SEROLOGIC GROUP	CLASSIFICATION TYPE
Adults	Post mortem, blood culture	1			D	H69D-5
	spleen	1	Alpha	-	D	H69D-5
	mitral valve	1			D	H69D-5
	blood culture	4			D	Lanc-3
	Ante mortem, blood culture	2	Alpha	-	D	H69D-5
	blood culture	1	Beta	+	D	Lanc-1
	blood culture	2	Alpha	+	D	Lanc-3
	blood culture	1	Alpha	-	D	Lanc-3
	blood culture	1	Alpha	+	D	D-76
	blood culture	2	Alpha	-	-*	-
Children	joint fluid	1	Alpha	-	-*	-
	Ante mortem, blood culture	2	Alpha	-	D	H69D-5
	blood culture	1	Gamma ₁	-	D	H69D-5
	blood culture	1	Alpha	-	-*	-

All strains insoluble in bile, none produced soluble hemolysin.

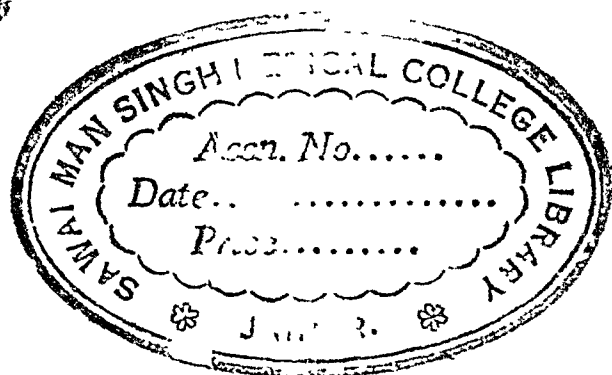
All strains except * reduced methylene blue.

*Classified tentatively as *Str. viridans* on basis of failure of hydrochloric acid extract (concentrated) to react with antisera for Lancefield Groups A to M.

from subacute bacterial endocarditis, are often serologically identical and frequently, as do most of the "enterococci," belong to Lancefield Group D.

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Clinical Reports

AORTIC HYPOPLASIA WITH ASSOCIATED VASCULAR AND GENITOURINARY ANOMALIES

REPORT OF A CASE WITH AUTOPSY

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HYPOPLASIA of the aortic system has been defined by Maude Abbott¹ as "that condition in which the lumen of the arterial vessels in the greater circulation remains abnormally small and the walls unnaturally thin and elastic." First described by Morgagni, in 1761, it received the attention of such men as Virchow, and is reported by Ikeda³ to have been the subject of some one hundred case reports by 1907. Since that time only sporadic cases have been reported,^{4,5} and, since 1933, the only report of which the authors are aware is that of Werley, Waite, and Kelsey.⁶ No attempt will be made to review the literature, which has been adequately reported in the papers of Burke,² Ikeda,³ and Werley.⁶ It is our purpose, however, to report an unusual case in which the presenting complaints were neurological, and in which a severe degree of cardiac insufficiency in a young man was apparently the result of a hypoplastic and anomalous arterial system.

CASE REPORT

History.—W. S. (Case 216553), a 31-year-old, white man, was admitted to the Strong Memorial Hospital on March 27, 1944, with a chief complaint of paralysis of the right side of the body of three weeks' duration. The patient stated that he had not felt well since the summer of 1942. At that time he was in Florida, and noted the gradual onset of fatigability, weight loss, lassitude, palpitation, and some numbness and tingling of the arms and legs. These symptoms continued, and in the spring of 1943 he returned to his truck farm outside Ithaca, New York. No history suggestive of any tropical disease could be elicited. Lassitude, anorexia, and decreased tolerance for work persisted, and, on Feb. 1, 1944, the patient consulted Dr. Simon Schmal of Ithaca. Examination at that time, according to Dr. Schmal's report, showed a pulse rate of 104 per minute and a blood pressure measurement of 105/80. The hemoglobin was 100 per cent, and serologic examination and urinalysis were negative. The patient returned on February 15, his systemic symptoms slightly improved, but he complained of deafness in the right ear, mumbled speech, and paresthesias of the right hand and arm. These had developed following a severe emotional upset. In the two days following this visit, several "nervous spells" occurred, during which, for a short time, he was unable to talk.

On March 5, 1944, about three weeks later, the patient developed aphasia, difficulty in swallowing, and a complete right hemiplegia, without loss of consciousness. He was referred to Strong Memorial Hospital for study on March 15, but on the day before his scheduled admission to the hospital, he had an episode of unconsciousness and severe coughing with production of one-half cupful of dark red blood. His temperature rose to 104° F., and he was acutely ill. Roentgenograms showed infiltrations in both lobes of the left lung and marked cardiac enlargement. A diagnosis of bronchopneumonia was made at the time, and a second x-ray examination, one week later, revealed definite clearing of the infiltrations and a reduc-

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tion in heart size. During the acute stage of the illness, signs of heart failure developed, and he was given small doses of digitalis. By March 27, the patient was deemed sufficiently recovered for transfer to Rochester.

The past history contained few positive findings. There had been a "tuberculous gland in the neck" when the patient was 18 months old and what was apparently an uncomplicated pneumonia ten years before admission. Otherwise, he had led an active, vigorous, outdoor life, and had done considerable mountain climbing as a pastime. At various times he had been a preacher, farmer, and somewhat of a recluse. There was no history of rheumatic fever or chorea, and there had been no dyspnea, orthopnea, or ankle edema prior to the present illness. It was noted on admission that the patient's voice was unusually high-pitched, and members of the family declared it had always been so.

There was no family history of nervous disorders or congenital anomalies of any sort. The father and mother were living and in reasonably good health, though the patient's mother had hypertension. A sister was living and well.

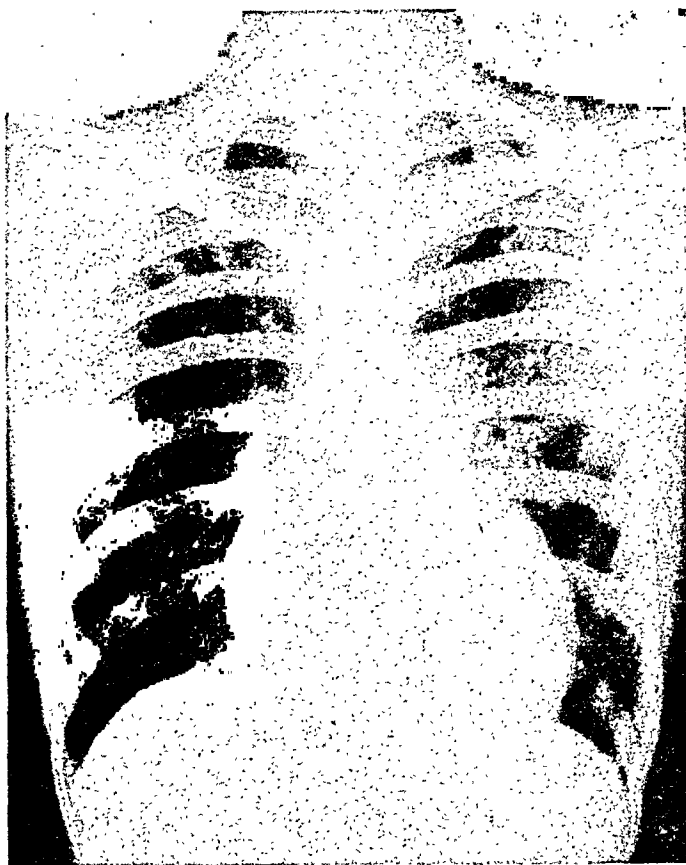


Fig. 1.—Teleroentgenogram taken March 28, 1944. Note the enlarged globular heart with small inconspicuous aorta.

Physical Examination.—On admission the temperature was 37° C., the pulse was 82 per minute, the respirations were 16 per minute, and the blood pressure measured 130/88 in both arms. The patient was a malnourished individual who appeared chronically ill and could not move the right arm or leg. The voice was unusually high pitched. The patient was oriented and cooperative. The skin was dry and coarse. No petechiae were noted, and there was normal distribution of body hair. The left pupil was somewhat smaller than the right, but both reacted to light and accommodation. The fundi were normal. The tongue was somewhat redder than normal, and cheilosis was noted at the corners of the mouth. There were no lesions on the buccal mucous membranes. The trachea was in the midline. The lungs were clear to percussion and auscultation. The cardiac point of maximal impulse was in the left anterior axillary line, and the heart was diffusely enlarged in nondescript fashion. The heart was overactive, and the sounds were loud. No thrills, rubs, murmurs, or irregularities were detected. No abdominal organs were palpable, and there was no tenderness. No sacral edema was noted. Both testicles were in the scrotum, and both were thought to be of normal size and consistency. The left foot was somewhat colder than the right. The dorsalis pedis pulsation was absent on the left, while the posterior tibial and popliteal pulsations were only barely palpable. All peripheral pulsations were of normal strength in the right leg. The blood pressure was 110/70 in the left leg and could not be obtained in the right. The left

radial pulse was appreciably weaker than the right and the radial artery was in a somewhat anomalous position. There was considerable atrophy of the interosseous muscles of the right hand and the muscles of the right arm. The neurological examination revealed a right hemiplegia. A right lower facial paralysis was apparent. The tongue deviated to the right. Abdominal and cremasteric reflexes were present on the left, but none could be elicited on the right. The deep reflexes were hyperactive on the right side, while the ankle jerk and knee jerk were absent on the left. There was a positive Hoffman's sign on the right but Babinski's sign was absent. Some motor aphasia was present.

Laboratory Findings and Course in the Hospital.—The Wassermann test was negative. The erythrocyte count was 4 million and the hemoglobin 13 Gm. The leucocyte count was 9,000 per cubic millimeter, with 70 per cent polymorphonuclear cells and no eosinophiles. The urinary findings were negative except for a rare red blood cell in the sediment, and the findings continued similar throughout the patient's stay in the hospital. The examination of the stool gave a negative test for blood, and no parasites were found, either on direct examination or by the zinc flotation method. A lumbar puncture was done, and the spinal fluid showed no increase in cells or abnormalities in dynamics. The spinal fluid serologic test was negative, and the total protein was 25 mg. per cent. Numerous roentgenograms were taken, and the following findings were reported: *Posteroanterior film of the chest:* The heart was enlarged, globular in shape, with well-rounded borders. The transverse diameter was 15.8 centimeters. The transverse diameter of the chest, at the level of the diaphragm, was 26.8 centimeters. The aorta was inconspicuous and not visualized beyond the shadow of the spine or sternum. *Fluoroscopy:* Fluoroscopy in the supine position indicated all chambers share in the cardiac enlargement. Good pulsations were present at all borders. The aorta was not visualized, and no aortic indentation was seen on the barium-filled esophagus. *Skull:* Negative examination. *Abdomen* (film of kidneys, ureter, and bladder): The left kidney was outlined normally. The right psoas muscle and the right kidney were not visualized.

Two electrocardiograms were taken and showed extreme right axis deviation, the first tracing having an axis of 150 degrees and the second 80 degrees. Aside from a tachycardia of 120 per minute in the second tracing, there were no other significant findings. Repeated blood cultures were negative, and a muscle biopsy, taken from one gastrocnemius muscle, showed no evidence of periarteritis nodosa. Circulation times were measured but were considered inaccurate because of undependable responses from the patient.

The patient had an essentially afebrile and uneventful course for the first twelve days of admission, and injection of diodrast was contemplated for the purpose of visualizing the aorta. The only change in this period was recovery of a minimal amount of function in the right leg. On April 10, however, the patient began to feel poorly and coughed up a small amount of fresh blood. Some cyanosis of lips and nailbeds was noted. The temperature and pulse increased, and a loud gallop rhythm was heard over the sternum. A roentgenogram taken at this time showed an infiltration in the right lung field, thought probably to be an infarct. A sputum examination revealed only *Streptococcus viridans*, *Staphylococcus albus*, and diphtheroids bacilli. The temperature continued to rise, and the administration of sulfadiazine was commenced. The pulse was maintained at about 120 per minute. Icterus developed, and it was felt that the patient was having multiple pulmonary infarcts. Medication with sulfadiazine was discontinued, and, during the last twenty-four hours, signs of cardiac failure were noted. The patient was digitalized and placed in an oxygen tent, but he expired on April 17, 1944.

Autopsy Findings (Case A8542).—A complete autopsy was done. All organs were carefully studied, but only the gross pathologic changes and pertinent negative findings are presented.

The body was that of an extremely emaciated 31-year-old white man. The skin was jaundiced, particularly over the face and neck, and the sclerae showed pronounced icterus. The left pupil was 2 mm. in diameter, and the right, 4 millimeters. There was no clubbing of the fingers and no edema. The peritoneal cavity contained about 150 c.c. of clear, light yellow fluid. The left pleural cavity contained about 600 c.c. of cloudy, yellowish-brown fluid, and the right pleural cavity about 100 c.c. of the same type of fluid. There were a few easily broken adhesions, bilaterally. The pericardial cavity contained about 125 c.c. of light yellow, slightly cloudy fluid.

The heart weighed 490 grams. The subepicardial fat was somewhat decreased in amount. There were two or three small soldier's plaques which were less than 1 mm. thick and did not extend into the musculature. The chambers were all extremely dilated, and the ventricles were pear-shaped. In the auricular appendage of the right heart and adherent to the muscular trabeculations of the left ventricle, there were a few small thrombi. In the

center of the foramen ovale, there was a small perforation about 1 mm. in diameter. The ductus arteriosus was demonstrated to be closed. The endocardium was smooth throughout. Beneath the surface of the ventricular endocardium there were a few, diffusely scattered, yellowish, sharply circumscribed areas, 1 to 3 mm. in diameter. These were less than 1 mm. thick but extended somewhat into the musculature. The tricuspid and mitral valves were dilated, but all valves were normal. The left ventricular wall was 0.8 cm. in thickness, and the right was 0.3 centimeter. There were no areas of infarction or thrombosis. The coronary arteries showed no abnormalities.

The aorta was of good elasticity and showed no degenerative changes. The aortic valve was 7.5 cm. in circumference. The aorta, immediately above the aortic valve, was 5 cm. in circumference. At the apex of the arch, it measured 3.2 cm., and in the distal descending portion of the arch, it measured 3.2 centimeters. The caliber became narrower where branches in the thoracic and abdominal cavities were given off. At about the level of the third lumbar vertebra, it bifurcated. The left branch was about 1.2 cm. in circumference, and the right branch about 0.6 centimeter. The right branch appeared to represent the right internal spermatic artery. Its main portion continued in the normal course of the spermatic artery but, about 10 cm. from its origin, it gave off a branch which was of larger caliber and 1 cm. in circumference. This appeared to represent the right common iliac artery. On the left side, about 5 cm. from the bifurcation of the abdominal aorta, a second bifurcation occurred: one branch, which was 1 cm. in diameter, apparently represented the left common iliac artery, and the other, the mid-sacral artery. The latter was about 0.8 cm. in circumference. The hypogastric arteries were not identified. No anomalous veins were noted.

The left lung weighed 340 grams, and the right, 480 grams. The upper lobes were crepitant and flabby. The right middle lobe and the lower lobe were firmer in consistency, and many firm, nodular areas could be palpated beneath the pleura. On section, these were seen to extend into the parenchyma of the organ. They were fairly sharply circumscribed from the surrounding parenchyma and were of grayish to dark red color. Bloody fluid could be expressed when the lung was squeezed. On section of the lungs, the upper lobes were of grayish color and air-containing. The right middle lobe and both lower lobes were of a pinkish color.

The spleen weighed 180 grams. There was an old area of infarction which had been replaced by fibrous tissue. The organ was congested.

The liver weighed 1,210 grams. The edges were very sharp. There was a reddish mottling evident through the capsule. On section, the central areas were dark red and somewhat depressed, and were fairly well demarcated from the surrounding yellowish-tan portal areas. The organ was firm in consistency. Certain portal areas, especially near the surface, seemed to be reduced in size, and there was a network-like pattern of a reddish color.

The left adrenal was of normal size and shape. The right adrenal was adherent to the diaphragm and was flat in outline. Its dimensions were 3 by 3 by 4 centimeters. On section, it appeared to be normal.

The right kidney was absent. The left kidney weighed 245 grams. It was of somewhat crescentic shape with the concavity directed toward the aorta. There were remnants of fetal lobulations. The calices, pelvis, and ureter were normal. There were two arteries supplying this kidney. The superior vessel appeared to be the chief source of supply and was about 0.5 cm. in diameter. A second vessel arising from the aorta, about 2 cm. below the first, was about 2 mm. in diameter.

Only the left half of the trigone of the urinary bladder was present. The prostate was normal.

On the right side, the vas deferans arose at the epididymis. About 4 cm. from its origin, there appeared to be occlusion of the lumen because the milky, fluid contents could not be squeezed beyond this point. The vas deferans coursed in the spermatic cord through the inguinal canal and, as it emerged from the internal inguinal ring, became adherent to the anomalous right common iliac artery previously described. It then doubled back upon itself, again merging with the spermatic cord until it approached the epididymis. At this point, it once more turned upon itself and coursed up the spermatic cord to terminate in an aberrant seminal vesicle, located on the right anterolateral pelvic brim in the normal position of the common iliac artery. The right seminal vesicle contained fluid which was dark reddish-green and which closely resembled that which might be found in a liquified hematoma. The left seminal vesicle appeared normal and contained the usual light tan fluid. The testicles were both in the scrotal sac, and were of normal size and consistency. The tubular architecture appeared normal.

The brain weighed 1,300 grams. On cutting the left lateral ventricle, a cloudy grayish fluid escaped. There was diffuse softening in the medial portion of the left cerebrum, just adjacent to the sagittal fissure. The vessels appeared to be normal. Upon sectioning the brain after fixation, the large area of necrotic softening on the left side was found to extend from the genu of the corpus callosum posteriorly to the tip of the occipital lobe, on its medial aspect. There was destruction of the basal ganglia, including the thalamus on the left side. There was extension from the ventricle out to the cortex of the temporal lobe. The right cerebrum and the cerebellum were intact.

Histologic Studies.—Sections of all organs were examined routinely. Only the significant ones are described.

The epicardium and endocardium of the heart were slightly thickened in some areas. The muscle fibers were larger than normal, and there was a great deal of hydropic degeneration. There were small areas of fibrosis scattered throughout the myocardium. There were old organized and recent thrombi adherent to the endocardium.

Sections from several areas of the aorta showed normal architecture. Measurements of fixed sections of the aortic wall, mounted on glass slides, indicated that the thickness varied from 0.1 to 0.15 centimeter.

The lungs showed scattered patches of bronchopneumonia with many large clumps of bacteria in some areas. One pulmonary vessel contained a thrombus. The vessel wall at this point was partially destroyed and was infiltrated with many acute cells and a few round cells. Surrounding this vessel, many of the alveoli contained red blood cells, and there were areas of bronchopneumonia in which the alveolar walls were partially broken down. Many of the alveoli contained large numbers of macrophages. There were many polymorphonuclear leucocytes in the bronchi.

The spleen showed increased trabeculation and congestion.

The liver showed some surface atrophy, and many of the central areas were greatly congested, with atrophy of the cord cells in these areas. There was some fat in the cells of the portal areas.

The right seminal vesicle had thick fibrous walls, and the glandular epithelium was poorly developed. The left seminal vesicle and prostate appeared to be normal.

In and beneath the cortex of the brain, there were areas of marked disintegration of tissue. The cerebral vessels were congested.

The anatomic diagnosis was: anomalous vascular and genitourinary systems; hypoplasia of aorta; congenital absence of the right kidney and ureter; anomalous right seminal vesicle and vas deferens; cardiac hypertrophy and dilatation; focal myocardial fibrosis; mural thrombi, right auricle and left ventricle; infarct of left cerebrum, recent; necrotizing bronchopneumonia; acute bronchitis; fibrinous pleural adhesions, bilateral; hydrothorax, bilateral; atelectasis; hydropericardium; hydroperitoneum; congestion of viscera; central necrosis of liver; fatty liver; jaundice; pulmonary embolus; compensatory hypertrophy of left kidney; old infarct of spleen; and emaciation.

COMMENT

This case falls into the general category of those in which cardiac insufficiency has been the result, solely, of a hypoplastic arterial system. The diagnostic feature was a youthful patient, previously vigorous and without cardiac symptoms, who developed cardiac enlargement and severe insufficiency with a progressively downhill course. The cardiac enlargement was nondescript, there were no murmurs heard, and no valvular or congenital cardiac abnormalities were found at the post-mortem table. The coronary arteries, themselves, were normal. It is unusual in that the presenting complaint was that of a hemiplegia, which developed over a period of a few days, and in the occurrence of extreme anomalies of the genitourinary system. Abnormalities of the genitalia are common in aortic hypoplasia, but such extensive anomalies of the genitourinary tract, as presented here, have not been previously recorded, to the authors' knowledge. At the post-mortem table, the exact cause of cerebral infarction could not be ascertained. From the mode of onset it was felt that cerebral thrombosis, probably secondary to a small cerebral embolus, was the most likely explanation.

It was generally agreed, by all who saw the patient, that diffuse vascular disease of some sort was present, and periarteritis nodosa was considered as a possibility. The correct diagnosis was suspected antemortem by virtue of (1) the absence of the aortic knob roentgenographically and the absence of an aortic indentation on the barium-filled esophagus by fluoroscopy, (2) the non-descript, diffuse type of cardiac enlargement, without murmurs or demonstrable valvular disease, occurring in a young man, and (3) the evidence of anomalies of the peripheral arterial tree, as indicated by examination of the vascular supply to the extremities.

Although not suspected during life, the congenital abnormalities of the genitourinary tract are of interest, not only because of their bizarre character, but also because they suggest that, in this case, at least, the aortic hypoplasia represents a congenital abnormality and not a developmental arrest.

It is desired to call attention to the fact that, while significant aortic hypoplasia is a rare finding, it should be given more consideration than has been accorded it in recent years by the medical profession, and that it can be the only demonstrable cause of severe and fatal heart disease in young adults.

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TRAUMATIC RUPTURE OF BOTH VENTRICLES OF THE HEART

CASE REPORT

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THE importance of traumatic heart disease is being made manifest in recent years by the increased number of publications and more frequent recognition of this clinical entity.¹⁻³ This problem is frequently encountered in industry from a medicolegal standpoint. It is the purpose of the paper to present a case of extreme cardiac injury associated with little evidence of external trauma.

CASE REPORT

A Negro male, aged 21 years, without history or evidence of previous cardiac disease, was brought to the hospital and found to be dead on arrival. It was reported that this man had been pinned between the cabin and chain cable of a small crane ditchdigger. The chest

was compressed in an anteroposterior direction, at the level of the lower sternum (Fig. 1). Approximately four minutes elapsed before he could be freed.

Autopsy Report.—The necropsy was performed two hours after the accident. A small abrasion was present in the right infrascapular region over the eighth and ninth ribs, about three inches from the midline. There were also small depressions on the skin overlying the lower portion of the sternum just above the xyphoid process and extending to the left shoulder. The remainder of the remarkable findings were limited to within the abdomen and chest.

Examination revealed linear fractures of the right eighth and ninth ribs, two inches from their vertebral attachments. There was no evidence of injury to the underlying lung. The pericardial sac was markedly distended with a volume of liquid and clotted blood which

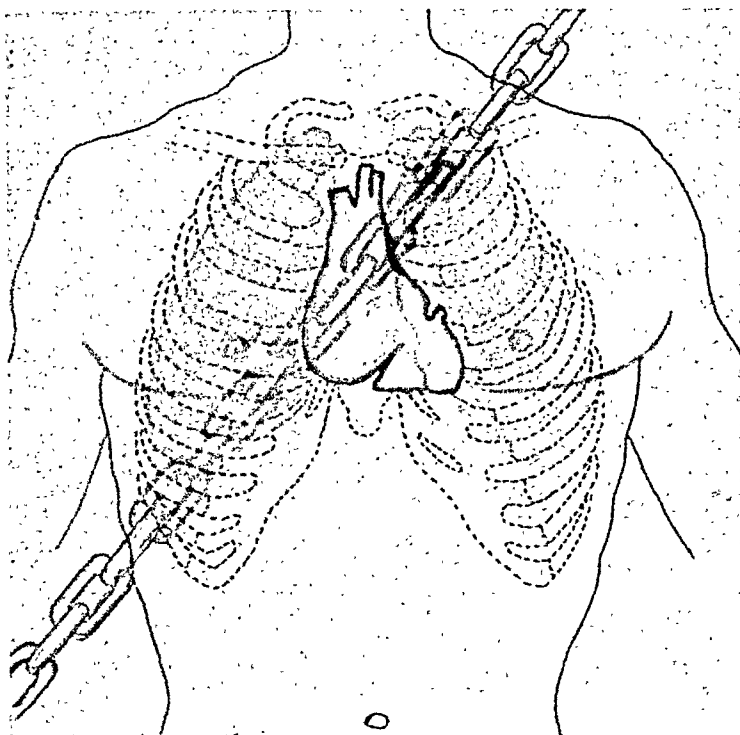


Fig. 1.—Schematic illustration showing location of compression force on chest resulting in rupture of the heart.

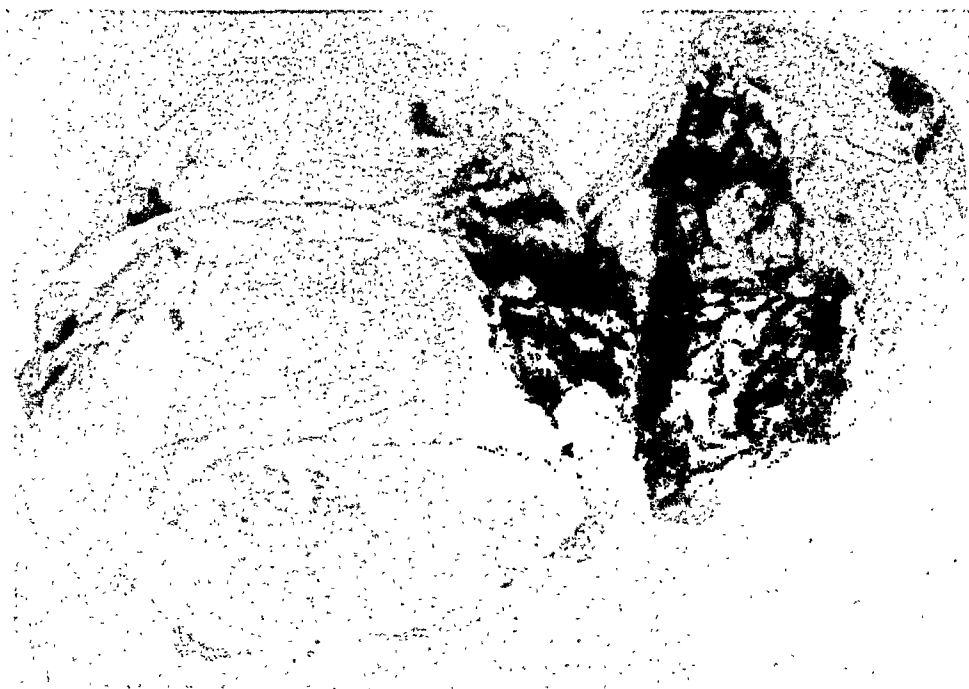


Fig. 2.—Traumatic rupture of both ventricles of the heart, posterior view.

measured 350 cubic centimeters. A large hematoma was seen protruding from the apex of the heart. A jagged tear, 11 cm. long, at the junction of the lower one-third and upper two-thirds of the posterior surface of the heart was present, which extended completely through both ventricles (Fig. 2).

On opening the abdominal cavity, 1½ liters of liquid and clotted blood were found. The liver was of average size and normal in appearance. On the posterior aspect of the right lobe of the liver there was an irregular laceration, approximately 3 cm. long and 3 cm. deep, which accounted for the intra-abdominal hemorrhage.

DISCUSSION

Traumatic heart disease has escaped recognition by many clinicians, chiefly because it was believed that the heart was well protected within the bony cage of the chest. The heart is particularly vulnerable because of its close approximation to the anterior chest wall. It has been found to suffer serious injuries from relatively minor trauma, both direct and indirect.

Beck, in 1935, made an exhaustive study of the mechanism causing traumatic heart disease.³ More recently the literature has contained numerous articles illustrating how varied this condition may be.^{2, 4, 5} Direct trauma to the anterior chest wall, such as that produced by a thrown ball, or a steering wheel, may produce contusion of the heart muscle. The resulting symptoms are not unlike those seen in acute myocardial infarction and may be accompanied by the corresponding physical signs and electrocardiographic changes. Patients suffering from contusion of the heart are likely to run a course similar to that in persons with acute coronary occlusion. Convalescence is usually uneventful but is, occasionally, complicated by myocardial failure. While spontaneous rupture is rare, it occurs most frequently in unrecognized cases during the second week following exertion.

Cardiac ruptures are also produced by broken ribs which are driven into the heart. Increased intracardiac pressure by application of compression forces to the legs and abdomen is capable of causing heart rupture.

A fourth mechanism causing bursting of the heart is that of compression between the sternum and vertebrae. A "blow out" results from the greatly increased intracardiac pressure, caused by constriction of the great vessels at the base of the heart. It is believed that this latter explanation is illustrated by this case report. The work of Bright has demonstrated the ease with which nonpenetrating wounds of this type may injure the heart muscle.⁶

World War II exposed large groups of persons to compression types of injuries. Ever increasing speed of transportation, both on the ground and in the air, will undoubtedly result in a greater incidence of traumatic heart disease.⁵ The presence of more obvious injuries, such as fractures or lacerations, should not lead the physician to assume that the cardiovascular system has escaped damage.

CONCLUSIONS

1. A case report of traumatic rupture of both the right and left ventricles with minimal evidence of external injury is presented. Search of the literature fails to reveal a similar lesion of this extent.

2. Traumatic heart disease is not uncommon and is apparently being recognized with increasing frequency.

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ISOLATED MYOCARDITIS PROBABLY OF SULFONAMIDE ORIGIN

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ISOLATED myocarditis is a pathologic term indicating an inflammatory process localized in the myocardium to the exclusion of the pericardium, endocardium, and (in the opinion of some) other tissues of the body. At present, most generally accepted entities of myocarditis are excluded; therefore, the etiology of isolated myocarditis itself must be unknown. This disease most often begins with a chill followed by dyspnea, precordial distress, and weakness with a rapidly progressing myocardial failure of undeterminable cause, often culminating in sudden death (Magner,¹ Helwig and Wilhelmy,² and Major and Wahl³). Subacute and chronic forms lasting months are recognized by Simon and Walpaw.⁴ This uncommon condition is rarely diagnosed before death.

Various etiological agents such as unknown viruses, peculiar hypersensitivities, vitamin deficiencies, and reactions to chemicals have all been suggested. Many of the cases presented to date have been associated with clinically classifiable inflammatory diseases including influenza, pneumonia, scarlet fever, typhoid, phlegmon of the foot, and gonorrheal urethritis. To include these cases in a classification of isolated myocarditis, one must assume that known bacteria and viruses did not cause the myocarditis or else the definition given above must be broadened. Animal experimentation⁵ may be of aid in clarifying the probable variety of causes.

A considerably varied histopathologic picture has been described in the literature as identifying isolated myocarditis or one of its several synonyms (Fiedler's, primary interstitial, circumscribed, diffuse idiopathic, productive, pernicious, and eosinophilic myocarditis). The disease has been divided into two distinctly different types, the granulomatous and the diffuse. In the first, the histologic change might well be confused with certain cases of tuberculosis, syphilis, tularemia, and mycosis. The difference is that the exact etiology cannot be proved in isolated myocarditis. Further, the patient should not have any known specific disease elsewhere in the body which might cause a granulomatous change in the myocardium. In this type one would expect patchy isolated lesions with a prominent fibrous element and inflammatory cells, possibly including lymphocytes, plasma cells, eosinophiles, monocytes, and giant cells in varied proportion.

The second, and more frequent, diffuse variety of isolated myocarditis has been described by Covey⁶ as showing a common microscopic pattern with minor variations and by Saphir⁷ as being mimicked by so many known inflammatory

diseases of the myocardium that it cannot be considered to have a characteristic histology. There is not only an interstitial but also a parenchymal reaction in some cases. The interstitial tissues are diffusely infiltrated by varying numbers of macrophages, lymphocytes, eosinophiles, and neutrophils, and there are varied amounts of diffuse fibroblastic reaction. Changes in muscle fibers are frequently described in this type of isolated myocarditis. They include focal areas of swelling, necrosis, sarcolysis, myolysis, "granular decomposition," and "explosive necrobiotic" changes.

French and Weller⁸ have reported 126 cases of interstitial myocarditis associated with sulfonamide therapy. They further reproduced an eosinophilic type of diffuse myocardial reaction in animals given various sulfonamides in dosages comparable to those given to human beings.

CASE REPORT

A 43-year-old man was first seen by one of us (S. G. S.) in his hotel room at about 3:00 P.M. on Oct. 23, 1943, five hours before his death. He stated that he had been ill with the "flu" for the past week or ten days. Just prior to his calling a physician he had been nauseated and had vomited profusely. The vomiting was not of a projectile type but was very copious. He suffered from a severe chill of malarial type which lasted for five minutes and he could not keep himself warm in spite of several extra blankets. In view of his extreme discomfort and condition, hospitalization was advised at once. He was admitted to St. Luke's Hospital at about 4:30 P.M. The physical examination, both at the hotel and the hospital, revealed the temperature to be 103.4° F. The pulse was 120 and the respirations were 24 per minute. The systolic blood pressure reading was 120 mm. and the diastolic was 84 mm. of mercury. His hair was sparse on the crown. The eyes, ears, nose, and throat were all essentially normal. Examination of the heart revealed no murmurs. Its rate was regular. The tones appeared to be of a distant type and seemed impaired in quality. There were no râles or other changes in the lung fields. No masses were palpated in the obese abdomen. There was no tenderness or rigidity. The rectal examination was negative. No edema of the extremities was noted. There was no urethral or prostatic discharge. The patient felt fairly comfortable after his hospitalization, and his only request was for sleep because he was completely fatigued.

A urinalysis revealed an amber urine with a pH of 5; specific gravity of 1.003; albumin, 4 plus; and sugar test, negative. Microscopic examination of the urine revealed 20 to 25 red blood cells and 8 to 10 white blood cells per high-power field. The hemoglobin was 93 per cent or 13.25 grams. The red blood cells numbered 4,620,000 per cubic millimeter; the white blood count was 12,400, with the following differential count: nonsegmented polymorphonuclears, 23 per cent; segmented polymorphonuclears, 62 per cent; and lymphocytes, 15 per cent.

Because of the very severe chill, indicating a possible blood stream infection, a blood culture was taken immediately after admission. After nineteen days of aerobic and anaerobic culture there was no growth. A definite diagnosis was not made on admission although it was assumed that the patient might be suffering from influenza, which was prevalent at that time, and probably also had a blood stream infection.

The patient revealed that, on October 5, he had had extramarital relations with a woman proved later to have gonorrhea. Because of this exposure he had been advised by a physician to take sulfadiazine. He had been taking 15 grains three or four times a day since October 14 (ten days), without medical supervision. There was no past history of any heart disease.

No medication was given the patient while in the hospital because it was the feeling that the sulfadiazine itself might possibly have contributed to his condition. Until a more definite diagnosis was made, therapy did not seem to be indicated. At about 8:00 P.M. on October 23, about four hours after admission, the nurses, in making routine rounds, found the patient dead.

Autopsy Findings.—This 43-year-old, well-developed and slightly obese white man measured 67 inches in height and weighed about 200 pounds. The only outstanding gross pathologic change was in the heart, which weighed 460 grams. This increase in size was due mainly to enlargement of the left ventricle. However, there was a mild dilatation and slight hypertrophy of the right ventricle. The left ventricular cavity was moderately dilated.

Its walls were remarkably pale and somewhat mottled throughout. It was not of the usual flabby consistency of a severely degenerated myocardium but maintained its form fairly well and was not friable. The trabeculae carneae in both ventricles were fairly prominent. A careful search revealed no myocardial fibrosis, and there was no significant sclerosis of the three principal coronary arteries or their visible main branches. The auricular cavities were normal in size, and their endothelial linings were transparent. The four valves had no fibrosis or vegetations and were apparently competent. The pericardium was transparent and free from injection and adhesions.



FIG. 1.

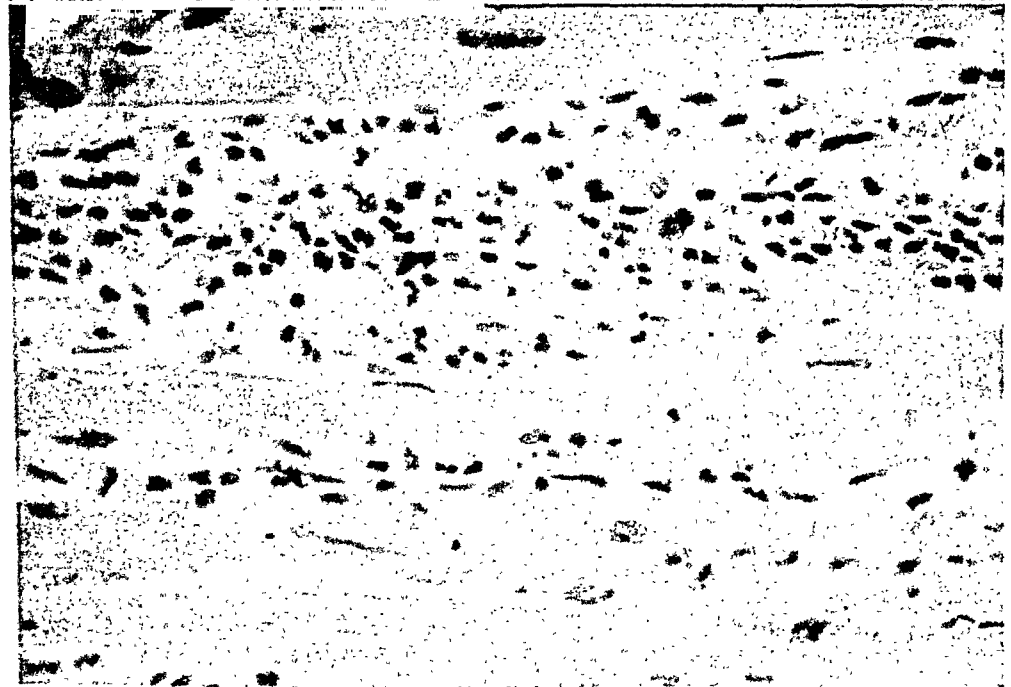


FIG. 2.

FIG. 1.—Diffuse infiltration of interstitial tissues of myocardium.

FIG. 2.—Swelling and granular necrosis of muscle fiber with neutrophilic reaction.

The other gross findings might well have been entirely secondary to a severe inflammatory disease. There was a moderate congestion and edema of the dependent portions of both lungs without gross evidence of chronic passive congestion or pleural fluid. The liver was somewhat pale, mottled, and flabby. It weighed 2,120 grams. The spleen, which weighed

320 grams, had an extremely soft, friable, granular, dark-red, cut surface. The kidneys, together, weighed 380 grams. Their parenchymal tissue was pale and slightly swollen throughout. The brain weighed 1,430 grams and appeared to have displaced much of the cerebral spinal fluid.

The microscopic study of the heart revealed an acute diffuse type of inflammatory process (Fig. 1), characterized mainly by an interstitial reaction with a predominance of neutrophiles in moderate numbers, swollen endothelial cells and fibroblasts in slightly increased numbers, and occasional eosinophiles, monocyctic phagocytes, and rare lymphocytes. There were also diffuse parenchymal changes, characterized by patchy irregularities in the staining of the muscle fibers, with occasional isolated, faintly granular changes in the muscle fibers. Rarely did one find a severely swollen segment (Fig. 2) with coarse, deeply acidophilic granules and beginning fragmentation. A neutrophilic reaction about these areas was noted. There were no Aschoff's bodies, and the reaction was no more severe about the smaller arteries than it was elsewhere in the interstitial tissue. The smaller arteries had no significant thickening of their walls. Special stains for bacteria failed to disclose their presence.

Moderate secondary toxic changes were evident in the liver, spleen, and kidneys. There was a mild, but distinct, increase in lymphocytic and monocyctic infiltration in the portal areas of the liver. No significant inflammatory cell reaction was found in the lungs; however, there was a diffuse congestion and edema.

DISCUSSION

The histologic changes in the myocardium in the case presented are typical of those described as a diffuse form of isolated myocarditis. We are much inclined to believe that they were due to the preceding sulfonamide therapy. However, influenza, gonorrhea (neither of which was proved to have been present), or unknown causes cannot be ruled out.

In cases previously reported of fatalities following sulfonamide medication, the question arises as to what part the primary condition, for which the chemotherapy was prescribed, may have contributed to the fatality itself as well as to the histologic changes. The presence of eosinophiles in the histologic picture in the myocardium suggests the possibility of hypersensitivity to the drug. This individual, unfortunately, continued to take the sulfadiazine as a prophylaxis for gonorrhea, which was never proved to have existed. The symptoms he suffered from can be well explained by the somatic deterioration from hypersensitivity to the sulfonamide. It is interesting, indeed, to note that, on questioning, no oliguria or anuria was reported by the patient. The microscopic examination of kidneys revealed no evidence of the usual kidney complications with deposition of sulfonamide concretions.

A brief discussion of the practical problems in the classification of myocarditis, in general, and isolated myocarditis, in particular, is pertinent. There are few pathologic terms in medicine used more loosely than myocarditis. Its use in connection with coronary sclerosis and the resulting complications has been gradually disappearing, almost to the vanishing point in current medical literature. However, it remains in frequent use among physicians in general. A greater problem at present is its use in connection with a variety of inflammatory, metabolic, degenerative, malignant, and deficiency diseases in which the clinician finds definite evidence of myocardial inadequacy complicating some known disease. In many of these disease processes the possibility of true myocarditis may exist. It is extremely difficult and often impossible to distinguish clinically between the far more common degenerative processes of the myocardium and the rare, truly inflammatory lesions. As a matter of fact, in some specific instances histopathologists are not entirely agreed as to when a "degenerative" process ends and an inflammatory reaction begins. Generally speaking, the presence of inflammatory cells, including the white cells of the blood, and the inflammatory cells developing from local tissue cells, are necessary

in the definition of an inflammatory process in any tissue of the body. There is undoubtedly a definite trend among clinicians to limit the use of the diagnosis "myocarditis" to conditions in which there is a histologically demonstrable inflammation in contradistinction to a degenerative change or a vascular disease of the myocardium.

The rarity of, and, to a greater extent, the lack of interest in, isolated myocarditis undoubtedly accounts for the present unsatisfactory understanding of the classification. There is good reason to believe that there are a variety of causes for the cases now published under this name. Therefore, it should be used purely as a pathologic term and not as the name of a disease entity. As each new cause for the myocarditis is proved it should be given a separate classification such as influenzal myocarditis or possibly arsphenamine myocarditis.

CONCLUSIONS

1. A case of diffuse isolated myocarditis is presented in which sulfadiazine may well have been the etiological agent.
2. An acceptable, clear-cut definition of isolated myocarditis cannot be arrived at after a review of the reported cases in the literature.
3. The name should be applied only to cases in which the etiological agent is unknown.
4. With an increased knowledge of the condition, it is likely that several disease entities may be distinguished.
5. The present widespread misuse of the term "myocarditis" is the result of long standing carelessness. It is a difficult clinical diagnostic problem to differentiate inflammatory from degenerative and vascular changes in the myocardium.

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MYOCARDIAL INFARCTION SUPERIMPOSED ON SHORT P-R, PROLONGED QRS COMPLEX

A CASE REPORT

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SINCE a search through the available medical literature failed to show any report of a case of "short P-R, wide QRS complex" complicated by myocardial infarction, it was thought worth-while recording such an incident.

CASE REPORT

A 41-year-old soldier with six months' service in the Army was admitted to the Station Hospital on March 1, 1943, because of a sudden episode of smothering and choking, followed by severe pain over the lower sternum, which had occurred on Feb. 28, 1943.

The patient had always been active in the past, working as a cook and miner. The family history was noncontributory. His past history was negative except for the fact that he had frequent paroxysms of rapid heart action, and two previous attacks of precordial pain with numbness radiating to both arms in June, 1942. These latter episodes lasted only a few minutes and caused the patient to remain home for a few days. This pain was similar in character to the one which caused him to seek admission to the hospital. There was no history of previous dyspnea or peripheral edema. His paroxysms of tachycardia were usually short in duration, would occur sometimes at rest, and were never incapacitating.

The patient felt quite well until February 28, when, while wrestling with some companions in his hutment, he suddenly felt "choked and smothered" and experienced severe pain over the lower sternum and epigastrium. He lost consciousness and later felt nauseated and had a "soreness" throughout his chest. He remained in bed most of the day, getting up, however, to eat dinner. He slept poorly that night. The next day he became extremely nauseated, felt very weak, but had no pain in the chest.

On admission, the patient did not appear to be in marked distress. There was no cyanosis. The thorax was emphysematous in type, and the lungs showed a few fine râles in the right anterior thorax from the fourth intercostal space to the costal margin. These findings were not constant. The heart was not enlarged to percussion. The sounds were of good quality with rate slow and regular. The aortic second sound was equal in intensity to the pulmonic second. No murmurs were heard. The blood pressure was 120/90. A small abdominal hernia was noted in the midline between the umbilicus and xiphoid process, but there were no adherent intestinal contents. Soon after arrival at the hospital, he had one episode of difficult breathing. An electrocardiogram was taken that morning.

The patient was kept in bed, given phenobarbital and aminophylline and frequent small feedings. The temperature rose on the second day to 99.8° F. by mouth. The blood pressure ranged from 110/60, on the day of admission, to 100/70 on the fifth day and remained at this level thereafter. He felt well all the time except for an occasional tight feeling in his chest. The lungs cleared completely, and at no time did he show evidence of congestive failure. The heart sounds remained of good quality with a slow regular rate. He had no episode of paroxysmal tachycardia or cardiac arrhythmia at any time. Occasionally a faint systolic murmur was heard at the apex, but a friction rub was never noted.

The urine showed no abnormalities. The initial leucocyte count, taken soon after admission, was 5,200 per cubic millimeter with 67 per cent polymorphonuclears and 33 per cent lymphocytes. The hemoglobin was 85 per cent. The sedimentation rate was 14 mm. in one hour. Ten days later the white blood cell count rose to 11,650 per cubic millimeter; the sedimentation rate remained at 14 millimeters. On the thirty-ninth day after admission, the white blood cell count was 18,600 and the sedimentation rate was 6. An x-ray examination of the chest showed the heart and lungs to be normal.

Electrocardiograms, taken on the day of admission, the third day, and the fourteenth day (Fig. 1), suggested a posterior wall infarct superimposed on a prolonged QRS, short P-R interval of the "Wolff-Parkinson-White syndrome."

About six weeks after admission an exercise test was performed with the patient going up and down a three-step stairway while holding an ice cube in his right hand. After eighteen trips he complained of a pressing and aching sensation over the precordium which lasted thirty seconds. This pain was similar in nature to that which had caused his admission but was shorter in duration. There was no radiation of this pain. About one week later, this test was repeated under similar circumstances and another episode of precordial aching was precipitated after twenty-two trips. This time the pain lasted twenty seconds. On the same day the test was repeated without the ice and the patient performed thirty-four trips before experiencing the same pain.

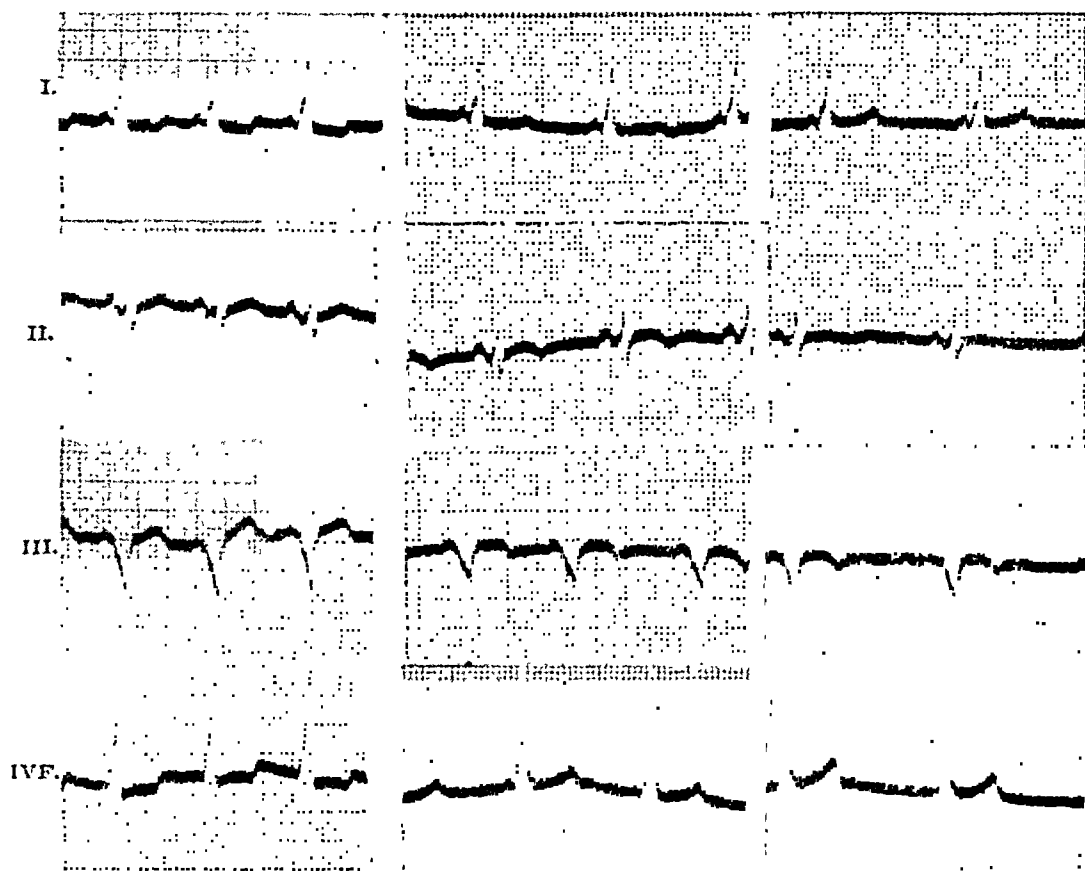


Fig. 1.—The first column of tracings on the left was taken on the day of admission: rate, 96; P-R interval, 0.09 second; QRS interval 0.11 second with slurring of upstroke of R₁ and downstroke of Q₁; left axis deviation; prominent S₂; T₁ diphasic; T₂ and T₃ upright and T₄ diphasic with S-T depression of 2 millimeters. The second column of tracings was taken three days later: T₁ upright, small amplitude; inversion of T₂ and T₃. These marked T-wave changes suggested a posterior wall infarct, superimposed on short P-R, prolonged QRS interval of the "Wolff-Parkinson-White syndrome." The third column of tracings was taken two weeks later: T₁ had become upright, low amplitude; persistent cove-shaped inversion of T₂. Wolff-Parkinson-White findings persisted unchanged.

Just prior to these exercise tests the white blood cell count was 11,350 per cubic millimeter, with 6 per cent stab cells, 63 per cent segmented forms, 29 per cent lymphocytes, and 2 per cent eosinophiles. About a week after the last exercise test the white blood cell count was 9,450, and the sedimentation rate was 16 mm. in one hour. The following week the sedimentation rate was found to be 20 mm. in one hour. Just prior to discharge the white cell count was 7,750, and the sedimentation rate had come down to normal.

The course of the electrocardiographic tracings during this period is recorded below (Fig. 2).

Two and one-half months after admission the exercise test was again repeated while the patient held an ice cube in the right hand. After forty-five trips precordial pain was reproduced which lasted fifty seconds. Precordial tracings which were taken immediately before and after the last test showed a marked inversion of the T wave but no deviation of the S-T segment during the pain (Fig. 3).

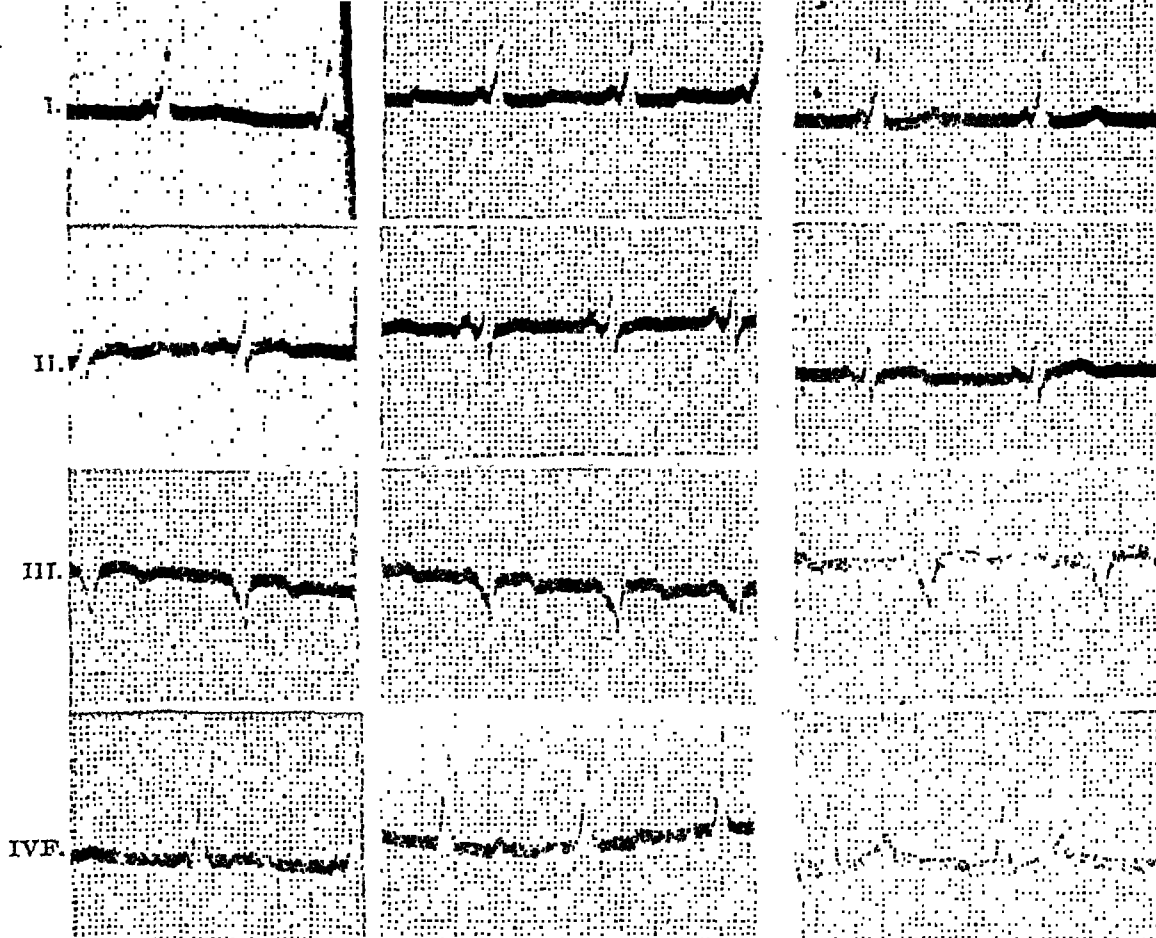


Fig. 2.—The first column of tracings on the left was taken one month later: little change over previous tracing except for slightly greater amplitude of T_2 . The second column of tracings was taken nine days later: T_1 , which had previously been upright and of low amplitude, diphasic; T_{4F} diphasic; T_2 and T_3 upright. The third column of tracings was taken about three weeks later: T_1 , T_2 , T_{4F} , upright; T_3 diphasic with coving. T_{4F} shows sharp upright pickup.

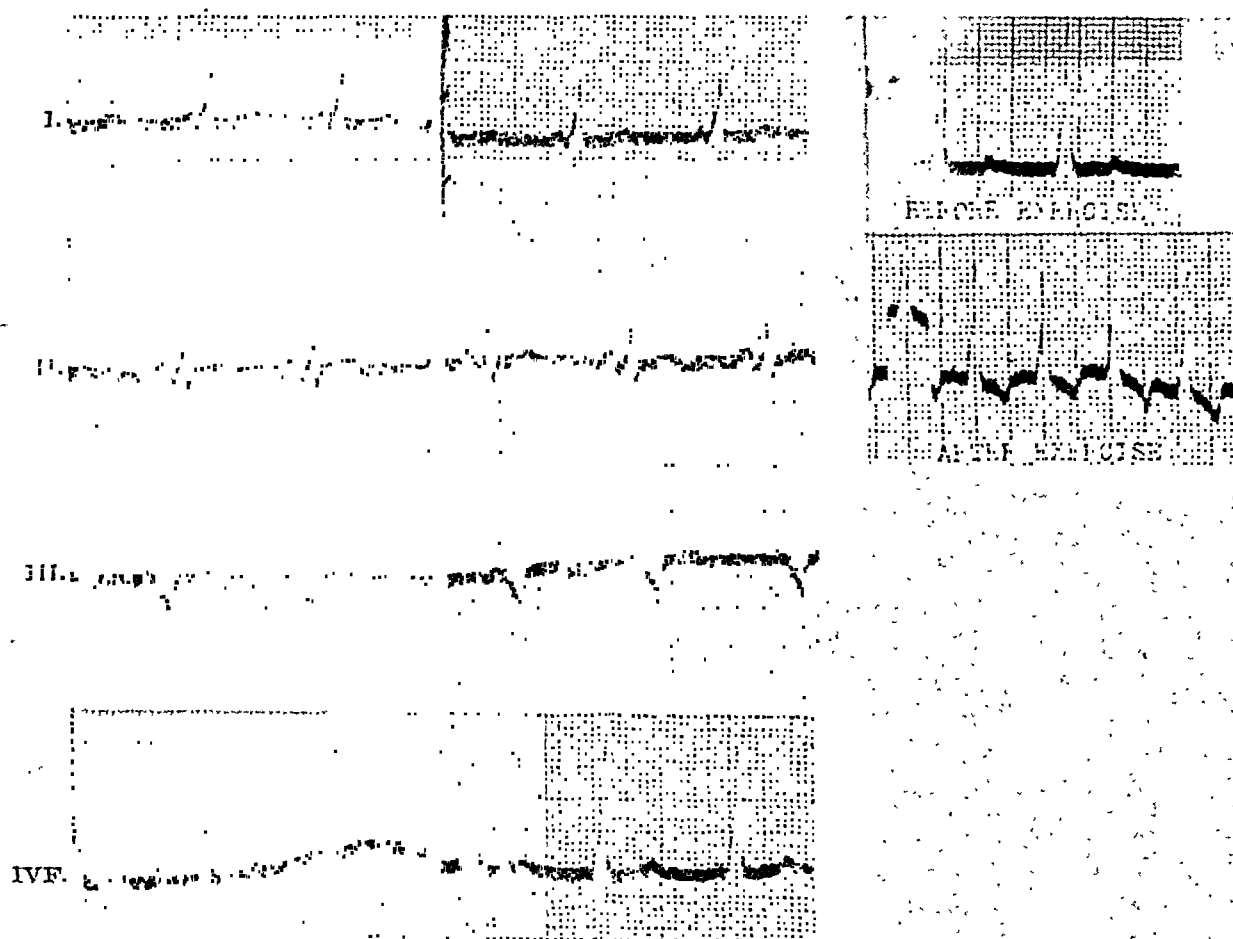


Fig. 3.—The first column of tracings on the left was taken two months after admission: inversion of T_3 less marked. The second column of tracings was taken one week later: no significant changes. In all these tracings there was a short P-R interval, widened QRS with slurred R_1 , and deep notched Q_3 . The third column of tracings was taken one week later: (Forty-five trips produced precordial pain lasting fifty seconds). Upper strip before test showed precordial tracing to be normal. Immediately after exercise lower precordial strip showed...

COMMENT

A consideration of the significance of the findings in this case resolves itself into two possibilities: 1. Is this short P-R interval, wide QRS complex, part of the electrocardiographic picture of myocardial infarction? 2. Is this a case of myocardial infarction in a person who had exhibited previously the Wolff-Parkinson-White syndrome?

For absolute proof of myocardial infarction, superimposed on a short P-R, wide QRS complex, there would have to be cardiographic evidence that this complex existed prior to the episode of myocardial infarction. The evidence does not exist in this case. However, the history of frequent attacks of paroxysmal tachycardia, along with the electrocardiographic changes, suggests that the Wolff-Parkinson-White syndrome was present prior to the coronary occlusion. Furthermore, we cannot find any literature on experimental or clinical bundle branch block or coronary occlusion with myocardial infarction in which the pathogenesis included shortening of the P-R interval along with the widening of the QRS complex.

It is concluded, therefore, that this patient probably represents a case of posterior wall infarction superimposed on the congenital anomaly of a short P-R interval and prolonged QRS.

Letters

To the Editor:

I have just read the article by J. A. Boone in the June, 1945, number of the *AMERICAN HEART JOURNAL*, page 751, entitled "Ventricular Fibrillation as a Complication of Hyperthyroidism."

It is my impression that a serious misinterpretation of the electrocardiogram has been made. Dr. Boone stated that the "Electrocardiogram (Fig. 1) showed auricular flutter, A-V dissociation, and intraventricular block. Lead II appears to consist entirely of a period of ventricular fibrillation." The article is titled and based upon this interpretation.

Clinically the patient presents the usual signs of auricular fibrillation—"rapid tumultuous heart action, grossly irregular, and the rate was 150 to 160 . . . the pulse deficit was 30 to 40." And the auricular fibrillation was of the paroxysmal type, since there was prompt restoration of the normal rhythm.

Leads I and III of the electrocardiogram show the characteristic findings of auricular fibrillation, namely absolute irregularity with irregular spacings of the ventricular complexes. There are here and there, small additional waves, which may be attributed to auricular activity (ff waves).

If these ff waves were due to auricular flutter, such waves, or accentuations of other waves, ought to appear regularly and periodically. They do not do so. The only real evidence for flutter is lacking.

If A-V dissociation were present, one would expect a ventricle beating without auricular control and, therefore, beating regularly. This is not so.

Lead II has been interpreted as ventricular fibrillation, and standing alone, it certainly "appears" to represent it; but standing between Leads I and III, it represents merely another aspect of rapid fibrillation. R_1 varies from 5 to 8 mm. in height. QS_2 varies from 3.5 to 5.5 mm. in depth. The algebraic sum (R_2) may vary considerably but can easily give some of the small and larger waves present in Lead II. The sum of the T_1 's and T_2 's, where the T_2 's are more greatly upright than the T_1 's are inverted, will also give positive waves. Fibrillary (ff) waves will explain the rest and add to the variations in height. It would be impossible to say which letter in Lead II is applicable to the different waves, but the diagnosis of *auricular* fibrillation is clear enough.

The condition present is the not infrequent one, in hyperthyroidism, of paroxysmal auricular fibrillation. It is not proper to allow the misconception implied in the title of this article to creep into the literature without correction.

(Signed)

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Aug. 28, 1945

To the Editor:

I should like to comment on the article, "Ventricular Fibrillation as a Complication of Hyperthyroidism," by J. A. Boone, which appeared in the *AM. HEART J.* 29: 751 (June), 1945.

In my opinion there can be no doubt that the electrocardiogram reproduced in Fig. 1, upon which the whole report is based, shows auricular flutter (rate 376) with varying A-V conduction and intraventricular block. The same mechanism is present in all leads.

Yet, the author interprets Lead II as ventricular fibrillation and calls it the "first proved instance of ventricular fibrillation in hyperthyroidism to be reported." Some more fundamental mistakes are revealed by the author's interpretation of Leads I and III of Fig. 1 as "auricular flutter, A-V dissociation and A-V nodal tachycardia with intraventricular conduction delay."

I think it is regrettable that this case of "ventricular fibrillation in hyperthyroidism" will now find its way into the *Index Medicus* and will be quoted in the literature.

(Signed)

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104 South Michigan Avenue
Chicago, Ill.
Sept. 11, 1945

Abstracts and Reviews

Selected Abstracts

Sulzer, R., and Duchosal, P. W.: Principle of Cardiovectography, *Cardiologia* 6: 236, 1942.

The Braun valves enable the combination of two linear vertical conductors and so the tracing of the horizontal projection of the electrical heart Vektor. The figures so obtained were called *Planogramme* (PG) by us. (Synonyms: vektodiagram, monocardiogram, triogram, etc.)

Owing to difference in form and conductivity of the tissue, the heart potentials in the human body are unequally distributed, wherefore, the law of projections, underlying the Einthoven triangle, is not quite perfect. The errors resulting therefrom are particularly apparent in planography. The present paper examines the matter of the distribution of the potentials in the human body for the purpose of drawing conclusions therefrom for the planogrammes and their interpretation.

These researches show that one of the most advantageous conductors consists in selecting for the horizontal conductors a plane situated below the heart. The distance, which guarantees agreement of the straight and oblique PG, stipulates that this plane should be situated in the region of the cristae iliacae.

The polarity of the conductors in planography and the manner of the connection of the Braun values are discussed. AUTHORS.

Mannheimer, E.: Calibrated Phonocardiography, *Cardiologia* 6: 281, 1942.

A new method, calibrated phonocardiography, is demonstrated and its value as clinical routine work is emphasized. AUTHOR.

Kartagener, M.: The Significance of Heredity for the Origin of Acquired Heart Disease, *Cardiologia* 6: 314, 1942.

The presence of coronary thrombosis was definitely observed once in two generations (mother and son, very similar electrocardiograms) and once in one generation, in two brothers in the early fifties. The one brother of the latter pair had at the same time a Buerger disease of the arteries of the extremities, which points to the possibility of the presence of arteriitis stenosans coronariae (von Albertini) as the cause of the coronary thrombosis. In a further observation, father and son, coronary thrombosis could be assumed with great probability.

The observation of sclerotic aorta insufficiency in two brothers, simultaneously suffering from kidney and bladder stone, is reported for the first time. AUTHOR.

Mola, B., and Acevedo, H. J.: The Electrocardiographic Diagnosis of Myocardial Infarction Complicated by Branch Block, *Rev. argent. de cardiol.* 11: 341, 1945.

Contrary to the opinion of many outstanding authors it is stated that in most cases of coexistence of bundle branch block and myocardial infarct, the electrocardiogram permits an easy recognition of the existence of the latter.

The diagnosis of posterior infarcts is made exclusively by the changes observed in the standard leads; in anterior infarcts by these and by changes in the precordial leads—sufficing in general C₁ and C₂ not being necessary to take multiple precordial leads.

In the standard leads the fundamental changes are seen in the S-T segment and T wave: their displacement instead of occurring in the same direction which is opposite to that of the greater wave of the QRS complex—as is characteristic of bundle branch block—occurs in alternative sense: if the S-T segment is elevated the T wave is inverted, and vice versa.

Furthermore, the character and direction of the convexity of the S-T segment are frequently inverted. Nonfundamental changes are the occurrence of Q_1 in left bundle branch blocks and Q_2 and Q_3 in right bundle branch blocks, as well as the appearance of M or W complexes of low voltage in DIII.

In precordial leads the fundamental change is the occurrence of a deep Q in the left leads, and the nonfundamental changes the elevation of the S-T segment and the T wave negativity, both of which are only observed in anterior infarcts.

Changes of the S-T segment and T wave disappear ordinarily in from fifteen to thirty days, those of the QRS complex, when present, are permanent allowing a retrospective diagnosis.

The practical importance of the diagnosis of the coexistence of bundle branch block and infarct is emphasized, especially so when the infarct is not accompanied by a typical clinical picture.

AUTHORS.

Neurath, O.: Is Digitalis Indicated in Myocardial Infarction? J. A. M. A. 128: 1016, 1945.

Digitalis alone used in congestive failure occurring with auricular fibrillation in myocardial infarction in thirty-two patients at the Los Angeles County General Hospital proved to be more harmful than beneficial. The hazard ordinarily considered the greatest, that is, the production of fatal ectopic ventricular rhythm with sudden death, was not in evidence. There was no increased hazard from cardiac rupture. The mortality was increased largely by the production of fatal emboli to the greater circulation. On the basis of these data, digitalis administered alone for the congestive failure associated with auricular fibrillation and myocardial infarction would seem contraindicated.

AUTHOR.

Rosenblatt, P., and Loewe, L.: Healed Subacute Bacterial Endocarditis, Arch. Int. Med. 76: 1, 1945.

Two cases of healed subacute bacterial endocarditis were encountered. Death in both instances was due to cardiac failure incident to aortic valvular insufficiency.

AUTHORS.

Homburger, F.: Effect of Sodium Salicylate on the Sedimentation Rate of Erythrocytes in Vitro, Am. J. M. Sc. 210: 168, 1945.

Sodium salicylate in vitro causes a marked reduction of the sedimentation rate of erythrocytes, particularly if it is accelerated. In fresh plasma this effect takes place at salicylate levels of about 90 mg. per 100 milliliters. In plasma which has been kept at room temperature for twenty-four hours, the effect takes place at levels of 25 to 30 mg. of salicylate per 100 ml. of plasma. When salicylate is left in contact with fresh plasma for the same length of time, the slowing of the sedimentation rate occurs at low levels. The standing of plasma at room temperature has an insignificant effect on the sedimentation rate of fresh red blood corpuscles in such plasma.

No demonstrable changes of plasma fibrinogen of red cells are caused by sodium salicylate and changes of the pH in the plasma do not account for the effect of sodium salicylate on the sedimentation rate. The effect is inherent in the salicylate radical, as sodium benzoate and sodium bicarbonate are ineffective.

It seems possible that this property of sodium salicylate, demonstrable in vitro, may partly account for the remarkable slowing of the sedimentation rate seen in some patients who receive salicylates.

AUTHOR.

Harris, T. N.: The Erythrocyte Sedimentation Rate in Rheumatic Fever, Its Significance in Adolescent and Overweight Children, Am. J. M. Sc. 210: 173, 1945.

Four hundred children, 215 of whom were girls, were observed during their convalescence from episodes of rheumatic carditis. In nine of these patients, eight girls and one boy, ranging from 9 to 16 years of age, the erythrocyte sedimentation rate remained persistently elevated long after the other signs, symptoms, and tests for active rheumatic infection had returned to normal or become stationary. These patients were ultimately allowed out of bed while the erythrocyte sedimentation rate was still elevated. Continued clinical observation followed the resumption of physical activity failed to reveal any indication that these children had been allowed out of bed prematurely.

Some theoretical and clinical implications of these data are discussed.

AUTHOR.

Levy, R. L., White, P. D., Stroud, W. D., and Hillman, C. C.: Transient Hypertension, J. A. M. A. 128: 1059, 1945.

In an earlier paper, based on an analysis of the medical records of 22,741 officers of the United States Army, it was shown that in the group with transient hypertension there was a greater incidence of later sustained hypertension and there were higher rates for retirement and for death with cardiovascular-renal diseases. Using the same material and indexes, the present study was designed to demonstrate possible differences in the prognostic importance of various systolic and diastolic levels of transient hypertension.

With respect to the later development of sustained hypertension and retirement with cardiovascular-renal diseases, all levels of transient hypertension, both systolic and diastolic, were significant. Of particular interest was the observation that slight degrees of elevation were important, even when the systolic level alone was involved. Of the greatest significance was a transient rise in diastolic pressure above 100 mm., especially as an early sign of subsequent sustained hypertension.

No significant differences were apparent between the various degrees of transient hypertension in relation to the death rates with cardiovascular-renal diseases. So, as is true for many other prognostic criteria applied to these conditions, the height of a temporary rise in blood pressure does not appear to foretell the severity or extent of the lesions which eventually are a cause of death.

The data given lend support to the view that transient elevations of blood pressure, above the upper range of normal, often represent an early stage of hypertensive vascular disease.

AUTHORS.

Rundles, W. R.: Hemorrhagic Telangiectasia With Pulmonary Artery Aneurysm. Am. J. M. Sc. 210: 76, 1945.

A case is reported of a patient with hemorrhagic telangiectasia who had suffered from repeated epistaxis from the age of 14 years, and in later life from gastrointestinal hemorrhage severe enough to produce a severe, incapacitating anemia. Multiple gastric telangiectasia were seen by gastroscopic examination. An aneurysm of the pulmonary artery was present which did not increase appreciably in size during a period of over seven years' observation.

AUTHOR.

Mason, J. M., III, and Giddings, W. P.: Experience With Lumbar Sympathetic Ganglionectomy for Wounds of Major Blood Vessels of the Lower Extremity. Surg., Gynec. & Obst. 81: 169, 1945.

Lumbar ganglionectomy, if it can be performed early, should be considered in the management of wounds from the bifurcation of the aorta to the bifurcation of the popliteal artery which jeopardize the circulation to the lower extremity. The real test may lie in its use in cases of severed popliteal artery, for very few extremities survive with injury to this vessel. Presence of an intact profunda femoris artery in the face of loss of the superficial femoral has been found to be no guarantee of the viability of the extremity. Collateral circulation of the lower leg has been found to be sufficient even in the presence of ligation of two of the three major vessels. It is felt that ganglionectomy will be less frequently indicated in injuries to vessels of the lower leg than in those of the thigh.

AUTHORS.

Lawson, H., and Rehm, W. S.: The Reversibility of the Cardiovascular Damage Done by Nearly Complete Exsanguination, Am. J. Physiol. 144: 206, 1945.

Barbitalized, moderately dehydrated dogs were almost completely exsanguinated by controlled bleeding in order to determine the liminal circulating blood volume. There appears to be a nearly straight-line relationship between the circulating blood volume in the intact unbled animal, and the liminal circulating volume. When the animals were kept alive by reinjection of blood, the liminal circulating volume as determined by a second, complete exsanguination was usually considerably elevated. The circulating plasma volume at the start of the final bleeding was usually less than the sum of the volume remaining at the end of the first plus the volume reinjected, by an amount which is nearly equal to the volume of extravascular fluid added during the first bleeding. It thus appears that nearly all the fluid which enters the circulation during the first bleeding leaves the circulation after the reinjection. If allowance was made for a systematic error in the measurement of circulating cell volumes, the cell volume at the beginning of the final bleeding appeared to be nearly equal to the sum of

the residual and the reinjected volumes. No reinjected cells thus appear to be withdrawn from the circulation. The average volume of blood drawn on the final bleeding was 9.7 c.c. per kilogram less than the sum of the residual bleeding volume, as estimated from control studies, and the volume reinjected. The elevation of the liminal circulating volume is just about enough to account for this loss of bleeding volume.

In similar experiments on dogs pretreated by intravenous injection of 15 c.c. per kilogram of 0.9 per cent sodium chloride solution, there was no evaluation of the liminal circulating volume of the final bleeding. The average volume of blood drawn on the final bleeding was only 4.4 c.c. per kilogram less than the sum of the residual bleeding volume and the volume reinjected. This moderate loss of bleeding volume following the reinjection appears to be due to a decline in circulating blood volume during the interval, and to a reduction in ability to replenish volume on the final bleeding. These changes cannot be attributed with assurance to any damaging effects of the first exsanguination, since the loss of bleeding volume in pretreated dogs is equally great if the first bleeding is terminated long before the exsanguination is complete. In dehydrated dogs the loss of bleeding volume is much less when the first bleeding is terminated earlier.

AUTHORS.

Lawson, H., and Rehm, W. S.: The Efficacy of Gelatin Solutions and Other Cell-Free Fluids in Reversing the Effects of Nearly Complete Exsanguination, *Am. J. Physiol.* 144: 217, 1945.

Barbitalized dogs pretreated by intravenous saline injection were almost completely exsanguinated by controlled bleeding and injected with various replacement fluids. The fatal hemorrhage volume four hours later was used as an index to the relative effectiveness of the fluids in reversing the effects of the first hemorrhage. As measured in this manner, the order of effectiveness of the fluids studied was: whole blood 3.9 per cent gelatin P-20 plasma and serum 3.45 per cent gelatin L-80 2.8 per cent gelatin B-20610-51 0.9 per cent sodium chloride. The gelatin solutions are approximately iso-osmolar, and have about the same colloidal osmotic pressure in vitro as dog plasma.

Dehydrated dogs (without saline pretreatment) were studied in similar experiments for evidence of damaging effects of gelatin P-20. The volume remaining in the circulation at death was not significantly greater than in dogs replaced with whole blood. Blood replenishment during the final hemorrhage was at least as great as in animals replaced with whole blood. The circulating blood volume maintained following the replacement was at least as great as that maintained by dogs replaced with whole blood. Replacement with higher concentrations of gelatin P-20 (6 per cent) produced larger circulating blood volumes. No evidence was obtained that the higher concentrations produced additional cardiovascular damage under these experimental conditions.

AUTHORS.

Frank, H. A., Seligman, A. M., and Fine, J.: Traumatic Shock, X. The Treatment of Hemorrhagic Shock Irreversible to Replacement of Blood Volume Deficiency, *J. Clin. Investigation* 24: 435, 1945.

The therapeutic value of various agents for the treatment of hemorrhagic shock, which is not responsible to the replacement of all shed blood, was tested under conditions calculated to avoid or to minimize the confusing effects of anesthesia, blood sampling, operative manipulations, and other forms of trauma. Utilizing the relatively simplified set of conditions described the following results were observed with the agents tested:

Massive infusions of saline may cause transitory improvement in circulation but do not cure hemorrhagic shock irreversible to transfusion.

Massive infusions of isotonic bovine albumin greatly increase the blood volume and may sustain the circulation for a time, but only rarely result in recovery. A marked bleeding tendency is produced by this therapy. Concentrated (25 per cent) bovine albumin solution in equivalent or greater protein content is of no benefit, even if supplemented by saline solution.

Large volume intravenous infusion therapy, using either saline solution alone or albumin in saline solution, is harmful by producing marked edema of tissues, serous effusion, venous distention, and widespread hemorrhage from small vessels.

Pitressin, with or without ergotamine, is of no value. The combination of pitressin with 5 per cent albumin solution is not beneficial. Paredrine causes an elevation of the arterial and venous blood pressure and no improvement in cardiac output. The duration of this effect is limited by the rapid development of unresponsiveness to the drug, and

survival time is not prolonged. Coramine increases skeletal muscle tone, but does not favorably influence the course of events.

The correction of acidosis by the administration of sodium bicarbonate with the initial transfusion does not alter the deteriorating trend of advanced hemorrhagic shock. Sodium acetate is of no benefit in the therapy of advanced hemorrhagic shock. Tuamine, given when the initial transfusion is failing, causes a transitory rise in blood pressure but the effect is brief. Survival time is not prolonged. "Potassium phosphate" intracisternally did not alter the deteriorating trend of hemorrhagic shock and at the same time produced undesirable cerebral excitatory phenomena.

It is the authors' view that advanced shock constitutes a state of progressive deterioration which is not amenable to the types of therapy now available, probably because fundamental biochemical changes have developed as a result of prolonged deficiency of capillary flow. These changes may result from injury predominantly involving one vital organ, such as the liver, or from widespread cellular damage.

AUTHORS.

Goldberg, M., and Fine, J.: Traumatic Shock, XI. Intestinal Absorption in Hemorrhagic Shock, *J. Clin. Investigation* 24: 445, 1945.

In hemorrhagic shock, the small intestine is progressively deficient in its absorptive capacity for water and isotonic glucose. After transfusion, whether effective or not, some improvement in this function may be observed, but full recovery is not observed within the time interval of these experiments.

The absorption of physiologic saline is not clearly affected by the institution of hemorrhagic shock until the advanced stage of shock is reached.

AUTHORS.

Hunter, J. B.: Observations on Ligature of the Patent Ductus Arteriosus. *Brit. M. J.* 1: 731, 1915.

Fourteen cases are reported in which ligation of a patent ductus arteriosus has been performed. Twelve cases were uncomplicated by infection, and in only two was endocarditis present. In ten cases the patients were female and the ages varied between 5 and 31 years. In the noncomplicated cases, the patients were all slightly stunted in growth, and the majority were breathless on exertion, but only one showed any signs of cyanosis. It is too soon to see what the ultimate fate of these cases may be. One of the children is now taking up tap dancing as a profession; the young male was accepted by the Service. The others have lost their breathlessness on exertion, and the earlier ones that have been recently reviewed have improved in general health and physique.

McCULLOCH.

Gottschall, E. Y., Laurent, D., DeKruif, P., Simpson, W. M., Kendell, H. W., and Rose, D. L.: The Effect of Artificially Introduced Fever on Humoral Antibodies and on Histamine Intoxication in the Guinea Pig. *J. Lab. & Clin. Med.* 30: 563, 1945.

An artificially induced fever temperature of 42.2° C. maintained for thirty minutes has no effect upon the humoral precipitin titer of guinea pigs immunized against horse serum.

The antiprotein titer of sensitized guinea pigs is not significantly altered by a fever temperature of 42.2° C. maintained for sixty minutes when the serum is titrated by a modified Praeger-Kuttner reaction.

A fever temperature of 42.2° C. maintained for thirty minutes suppresses histamine shock.

In vitro tests with surviving normal intestine exposed to histamine indicate that there is no contraction at 43.3°, 45°, or 46° C. than at 38.8° or 39° C. Response of sensitized intestine to the typical antigen (ovalbumin) is also decreased by temperatures of 43.3°, 45°, or 46° C.

The immediate type of reaction in the guinea pig's skin is suppressed by a fever temperature of 42.2° C. maintained for sixty minutes when the locally sensitized tissue is injected with histamine solution during hyperpyrexia.

AUTHORS.

Book Reviews

A PRIMER OF ELECTROCARDIOGRAPHY: By George Burch, M.D., and Travis Winsor, M.D., Lea & Febiger, Philadelphia, 1945, 215 pages, including table of contents, appendix, and index, 235 engravings.

The title of this book is not entirely adequate, as the work contains much more than on elementary discussion of electrocardiography. The authors obviously have considerable knowledge of the electrical phenomena responsible for the electrocardiogram, and, in this respect, the book is quite different from most available texts on this subject. In the presentation of electrocardiograms related to various cardiac conditions, emphasis is placed upon the reasons for the appearance of characteristic alterations in the tracings. This approach, in the opinion of the reviewer, is so far superior to the purely descriptive method, so often employed, that this book stands nearly in a class by itself.

The first chapter, which occupies approximately one quarter of the book, is largely concerned with a description of the elements which make up the normal electrocardiogram, discussions of the fundamental concepts relating to depolarization and repolarization and the flow of currents in volume conductors, and finally with a presentation of the standard limb leads and the electrical axis viewed from the standpoint of these basic considerations. The remaining four chapters take up important electrocardiographic conditions and include good discussions of precordial leads, the cardiac arrhythmias, and the ventricular gradient.

The changes produced by myocardial infarction are well presented although the reader might find the arguments easier to follow if all the discussions relating to this matter were in one section rather than being distributed in Chapters II, III, and V. Since the basic changes in the QRS complex, RS-T segment, and T wave due to acute injury, myocardial ischemia, and infarction are found in a more or less modified pattern in any lead that is clinically useful but occur in the purest form in precordial (or esophageal) leads, it seems logical to open the discussion of these matters by detailed descriptions of the alterations that are found in leads of the latter type. Changes to be expected in the standard limb leads may then be directly inferred if one remembers that anterior infarcts produce modifications in these leads only when the potential of the left arm is altered in the characteristic manner and posterior infarcts produce them, only when the potential of the leg is similarly changed.

There are not many features of this book with which one can violently disagree, but a few minor criticisms may be justified. The classification of complete bundle branch block into a typical and an atypical variety on the basis of the direction of the T waves is a bit arbitrary. As a matter of fact, activation or depolarization of the ventricles occurs in an identical fashion in the two groups. It is recovery and not activation which is atypical.

In the discussion of the method for taking precordial leads with the use of the central terminal, it is stated (page 112) that, since the sum of all the forces (currents) in a network flowing toward a single point is zero, the central terminal is, for all practical purposes, at zero potential at all times. While we believe the conclusion here to be a true one, unfortunately this question cannot be settled so easily.

It is perhaps to be regretted that no actual electrocardiograms are reproduced in the book. On the other hand, the entire approach is to explain why things occur and not simply to illustrate things that have happened. For this purpose, the numerous well-drawn figures and electrocardiograms serve admirably. As the authors remark in the preface, other books are available in which many well-reproduced tracings may be found. In the opinion of the reviewer, there are few other books that can offer as much as this one to the student really interested in the fundamental aspects of electrocardiography.

F. D. JOHNSTON.

Announcement

Due to conditions beyond the control of the editors and publishers, several issues of the JOURNAL are printed on an inferior grade of paper. Just as soon as the standard good grade of paper is available, its use will be resumed.

American Heart Association, Inc.

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THE American Heart Association is the only national organization devoted to educational work relating to diseases of the heart. Its activities are under the control and guidance of a Board of Directors composed of thirty eminent physicians who represent every portion of the country.

A central office is maintained for the coordination and distribution of important information. From it there issues a steady stream of books, pamphlets, charts, films, lantern slides, and similar educational material concerned with the recognition, prevention, or treatment of diseases of the heart, which are now the leading cause of death in the United States. The AMERICAN HEART JOURNAL is under the editorial supervision of the Association.

The Section for the Study of the Peripheral Circulation was organized in 1935 for the purpose of stimulating interest in investigation of all types of diseases of the blood and lymph vessels and of problems concerning the circulation of blood and lymph. Any physician or investigator may become a member of the section after election to the American Heart Association and payment of dues to that organization.

The income from membership and donations provides the sole financial support of the Association. Lack of adequate funds seriously hampers more intensive educational activity and the support of important investigative work.

Annual membership is \$5.00. Journal membership at \$11.00 includes a year's subscription to the AMERICAN HEART JOURNAL (January-December) and annual membership in the Association. The Journal alone is \$10.00 per year.

The Association earnestly solicits your support and suggestions for its work. Membership application blanks will be sent on request. Donations will be gratefully received and promptly acknowledged.

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No. 6

Announcement

SOME months ago, Dr. Fred M. Smith announced that he would be unable to continue as Editor of the AMERICAN HEART JOURNAL after the end of 1945. His resignation came as a great surprise, but the Directors of the American Heart Association could not feel justified in asking the continuation of the labors that he has performed so well and faithfully for eight years and reluctantly agreed to select a successor.

Only editors themselves and those in close touch with their activities can realize the enormous amount of time and energy that must be given to the successful accomplishment of their duties. Even when full use is made of associate editors and members of the Editorial Board, most of the responsibility for the selection and editing of papers and the determination of editorial policies falls upon the Editor-in-Chief and the one Associate Editor who serves directly with him. That Dr. Smith has recognized and lived up to the responsibilities of his position, no one who knows the AMERICAN HEART JOURNAL would question. He has more than justified his appointment eight years ago, and has made a lasting contribution to the cause of better medicine and better medical literature in the United States. In this, the final issue of the JOURNAL under his Editorship, the Directors of the American Heart Association wish to express their deep gratitude for his unselfish devotion and unswerving loyalty, for the time and effort that he gave so generously, and for the intelligent direction that has kept the JOURNAL at such a high level of excellence.

To his chief associates also, the Directors wish to express their heartfelt appreciation. Their splendid work receives little notice or praise; it is largely taken for granted, but without it the JOURNAL would suffer greatly. Upon the able shoulders of Dr. Horace M. Korns fell a great deal of the responsibility for the editing and revision of manuscripts and for the final form in which papers were published. Dr. Smith and other associates have testified repeatedly to the unselfish manner in which he devoted himself to this work. He has left the University of Iowa Medical School to enter the practice of medicine, and the best wishes of his associates go with him.

Dr. Hugh McCulloch has been an Associate Editor of the JOURNAL since its founding in 1925. For some years he has also been in charge of the important Department of Abstracts and Reviews. For his long, faithful, and distinguished service this public acknowledgment and expression of gratitude are most inadequate repayment.

In accordance with the agreement relating to this matter, the Board of Directors of the American Heart Association selected a new Editor-in-Chief, subject to the approval of The C. V. Mosby Company. Their selection was Dr. Thomas M. McMillan, of Philadelphia, who was accepted with enthusiasm

by the publishers. Immediately upon his confirmation, Dr. McMillan departed for conferences with the president and the staff of the Mosby Company and with Dr. Smith.

The Directors of the Association, regretful at the resignation of Dr. Smith, feel a great sense of relief and security in the knowledge that Dr. McMillan is to succeed him. Known in this country and abroad as a distinguished specialist in the field of diseases of the heart, he brings to his new position authority and prestige. Those who know him well realize that he has an unusual combination of qualities that would seem to fit him ideally for his new responsibilities. In addition to the unusual charm and graciousness which have endeared him to all his associates, he has keen critical ability, an extensive knowledge of medical literature, and a great fund of clinical experience and practical knowledge. He has accepted his new assignment with ardent enthusiasm and with an earnest desire to make the AMERICAN HEART JOURNAL one of the great medical journals of our time. It is with pride and complete confidence that the Directors of the Association present him to all readers of the JOURNAL and ask their full cooperation in the attempt to realize this laudable aim.

To Dr. Smith and his associate editors we say a reluctant farewell and extend our best wishes for continued success in their special work. To Dr. McMillan and the Editorial Board that he is now selecting we extend a most cordial welcome and promise full support in the months and years that lie ahead.

This announcement, properly devoted primarily to the departing and arriving editors, would be incomplete without a special word of thanks to The C. V. Mosby Co. and those members of their staff who are chiefly responsible for the publication of this JOURNAL. Both Dr. Smith and Dr. McMillan have spoken with warm appreciation of the cordiality and responsive cooperation of the publishers, and we have every confidence in their continued efforts to make the JOURNAL even finer.

H. M. MARVIN, M.D.
For the Board of Directors
American Heart Association

Original Communications

THE EFFECT OF SMOKING CIGARETTES ON THE PERIPHERAL BLOOD FLOW IN SUBJECTS IN THE OLDER AGE GROUP WITH CORONARY ARTERIOSCLEROSIS AND HYPERTENSION

HAROLD J. STEWART, M.D., HELEN S. HASKELL, M.D., AND
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NEW YORK, N. Y.

THE effect of the smoking of tobacco on the circulation has been the subject of many investigations. Its effects on the peripheral vascular system have taken on especial interest with the concern in the last few years about peripheral vascular diseases. In 1943, Evans and Stewart¹ reported observations upon the effect of the smoking of cigarettes on the peripheral blood flow in a group of young persons from 19 to 36 years of age. They found that smoking decreased the peripheral blood flow and increased the blood pressure and heart rate in these subjects. Similar effects were observed following the smoking of denicotinized cigarettes and those made of corn silk. It was suggested that these effects might be due to the effect of smoke on the respiratory tract. The literature bearing upon this subject was reviewed at that time. At the time this paper was written, a report by Goetz² which had been published two months earlier was not available to us. Goetz also found decrease in peripheral blood flow, as measured by digital volume, and attributed the effect also to "reflexes set in train by the irritation of smoke on the mucosa of the respiratory tract."

Since then, another excellent study of the effect on the circulation of smoking cigarettes and intravenously administering nicotine has been made by Roth, McDonald, and Sheard.³ They found the effects of smoking cigarettes similar to those which we recorded, in the measurements which they made which could be compared with our results, but did not observe the effects following the smoking of corn silk. Their experiments are not strictly comparable to ours because of different objectives and different techniques. We were interested in the average effect of smoking on the average peripheral blood flow; therefore, we recorded temperatures from eleven areas on the body surface. They were interested in the temperature of a finger and a toe as samples of the skin temperature and as an index of peripheral vascular constriction. They were of the opinion that the effects they observed were to be attributed to nicotine. These recent observations of Evans and Stewart,¹ Goetz,² and Roth, McDonald, and Sheard³ are all in agreement, however, about the general effects observed following the smoking of cigarettes.

Our earlier observations¹ were made on individuals in the younger age group, as were those of Roth, McDonald, and Sheard.² It seemed important to observe the effect of smoking on the peripheral blood flow in patients in the older age group, who were known to have vascular disease. Such observations

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form the subject of this paper. Patients were accordingly selected who were in the older age groups and who had known arterial disease: coronary artery disease, histories of coronary occlusion, hypertension, or arteriosclerosis. These patients showed no clinical evidence of peripheral vascular disease at the time these observations were made. In L. M., arteriosclerotic gangrene of the right foot required amputation forty-one days before these studies were made. The peripheral pulses were good in the left leg, and the skin temperatures of this extremity were warm. In the study reported here all the subjects smoked one brand of regular (standard) cigarettes. Studies were made of seventeen men, ranging in age from 38 to 81 years.

METHOD

The measurements of peripheral blood flow were made by means of a modification⁴ of the method of Hardy and Soderstrom.⁵ These observers have shown that, at temperatures below 28° C., the skin functions like a dead insulator when the subject is lying nude in the basal state, and that blood flow to the skin, thermal conductivity of the peripheral tissues, and vaporization are constant and minimum. With an increase in blood flow to the periphery, more heat is brought from the deeper tissues to the surface; this increases the thermal conductance of the superficial tissues, and, therefore, changes in thermal conductance become an index to peripheral blood flow. With this method, blood flow is expressed as a function of heat loss, surface area, *average skin temperature*, and rectal temperature. The method requires the recording of skin and rectal temperatures at known intervals, and of oxygen consumption, height, and body weight. The skin temperatures were recorded with a Hardy-Soderstrom radiometer from eleven points on the anterior surface of the body. The eleven areas were as follows: (1) forehead, (2) upper part of right side of chest, (3) lower part of left side of chest, (4) right side of abdomen, approximately at level of the umbilicus, (5) left arm, (6) left forearm, (7) dorsum of left hand, (8) upper part of right thigh, (9) lower part of right thigh, (10) leg, and (11) dorsum of left foot. This method measures the total amount of blood allotted to the periphery of the whole body, from the skin inward, for a depth of about 1 centimeter. It differs in this respect from those methods which measure the amount of blood flow going to a leg, arm, or finger. It is not possible to measure the amount of blood allotted to individual parts by this technique, but inferences can be made about this from the local skin temperatures. The resulting blood flow by this method is expressed in cubic centimeters per square meter of body surface. In addition to measurements relating to blood flow, the blood pressures and pulse rates were recorded between temperature readings.

PLAN OF PROCEDURE

The plan of procedure was essentially the same as that described in a recent publication.⁴ In the present study, measurements of skin and rectal temperatures were made at ten-minute intervals, instead of at twenty-minute intervals as in previous work. Each set of measurements covered approximately ninety minutes. The measurements of blood pressure and pulse rate were recorded during free intervals between temperature readings. The basal metabolic rate was measured before smoking, immediately after smoking, and again at the end of a morning's observations. For the period before smoking, the first value for basal metabolic rate was used in the calculation of peripheral blood flow. For the period during smoking, the average of the oxygen consumption before, and immediately after, smoking was used for calculating peripheral blood flow. For

the phase after smoking, the difference between the oxygen consumption immediately after smoking and that at the conclusion of the experiment was divided by the number of periods of peripheral blood flow measurements in such a way that it was properly apportioned among these periods. All except two patients (D. G. and C. T.) were smokers, and all inhaled while smoking. The subjects smoked, in succession, two-thirds of two cigarettes at their normal inhalation depth and frequency; exaggerated smoking was avoided. The duration of smoking varied with the subjects from sixteen to eighteen minutes. A room temperature of 27° C., with a relative humidity of approximately 45 to 50 per cent, was maintained. The cigarettes were of the same brand for all subjects. They were purchased on the open market.

Four sets of observations were made before smoking in all except one patient (A. K.), from whom three calculations of peripheral blood flow could be made. One or two sets of observations were made during smoking from which two or three calculations, respectively, of peripheral blood flow could be made which were influenced by smoking. Four or five sets of observations were made after the subject had stopped smoking, from which three or four calculations, respectively, of peripheral blood flow could be made. The measurements made before, during, and after smoking were each averaged and indicated by "before," "during," and "after" in Table I.

All observations were made in the morning before breakfast with the subjects in a basal metabolic state. After the constant temperature room had been brought to 27° C. and around 45 per cent humidity, the patient lay on the bed, nude, covered with a sheet for one hour, for the body to adjust to this temperature. A room temperature of 27° C. was selected to be certain that vasodilatation was present and available for constriction to take place later during smoking, and also in order to make the observations comparable to the ones on the younger individuals.

RESULTS

The data relating to M. K. (Fig. 1), 67 years of age, who had arteriosclerotic heart disease, coronary sclerosis, and enlargement of the heart, serve to illustrate the effects of smoking. The data for all subjects are summarized in Table I.

Effect of Smoking on Peripheral Blood Flow.—The peripheral blood flow decreased during smoking* in thirteen patients and increased* in four (Fig. 1, Table I). In those in whom the peripheral blood flow decreased while smoking, the peripheral blood flow continued to fall in the period after smoking, or began to return toward or to the control level. The four subjects in whom the average peripheral blood flow for the smoking period was increased showed, nevertheless, during smoking or in the period after smoking, single observations in which the peripheral blood flow was greatly decreased.

For this group of thirteen patients, showing decrease in peripheral blood flow during smoking, the average peripheral blood flow before smoking was 78 c.c. per square meter of body surface per minute; during smoking, 48 c.c. per square meter of body surface per minute; and after smoking, 59 c.c. per square meter of body surface per minute. For the four showing increase in peripheral blood flow, the average before smoking was 50 c.c. per square meter of body surface per minute; during smoking, 68 c.c. per square meter of body surface per minute; and after smoking, 89 c.c. per square meter of body surface per minute.

*These groups are designated the "decreased peripheral blood flow group" and the "increased peripheral blood flow group" in the rest of the paper.

The Effect of Smoking on Blood Pressure.—The systolic blood pressure rose in eleven instances in which the peripheral blood flow was decreased, and was unchanged in three patients, while the diastolic blood pressure rose in every instance. The average for the group showed a blood pressure of 134/79 before, 145/86 during, and 143/83 after smoking. In the four patients in whom the peripheral blood flow increased on smoking, the blood pressure did not show any significant change as the result of smoking, being 160/89 before, 161/93 during, and 160/90 after smoking (Table I).

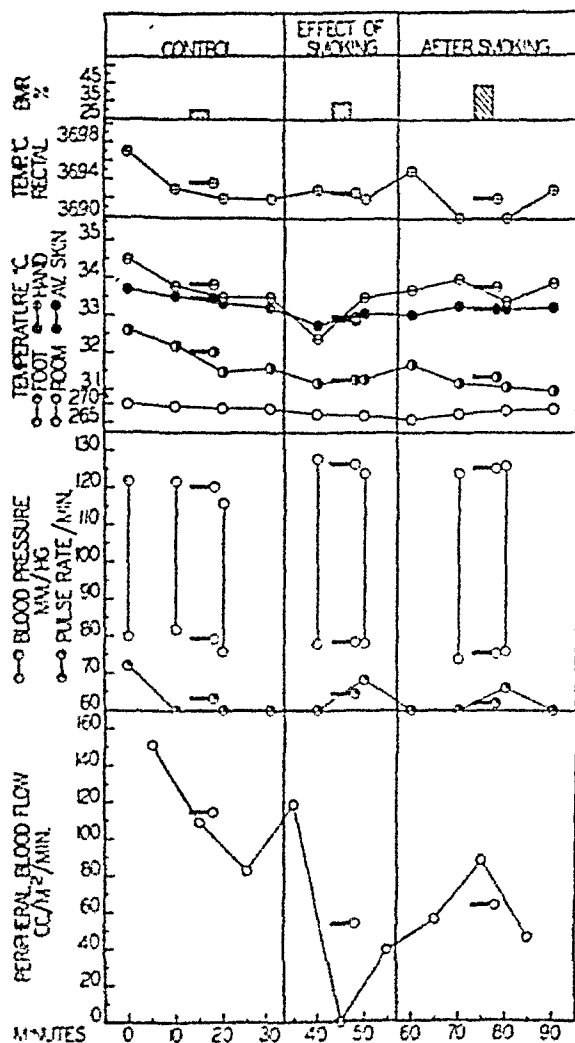


Fig. 1.—In this figure are shown the effects of smoking cigarettes on peripheral blood flow, average skin temperature, rectal temperature, temperatures of the hands and feet, pulse rate, blood pressure, and basal metabolic rate in M. K., 67 years of age, who had arteriosclerotic heart disease, coronary artery disease, and enlargement of the heart. All of the measurements of the peripheral blood flow, temperatures, etc., are recorded in the figure. The averages for each of the periods, namely, before, during, and after smoking, are indicated by solid bars with the appropriate symbols. The peripheral blood flow undergoes fluctuations from one ten-minute interval to the next as has already been described by Stewart and Evans.¹

The Effect of Smoking on the Pulse Rate.—The pulse rate increased in eight patients and was unchanged in five in the group showing decrease in peripheral blood flow as the result of smoking; the averages for the whole group were 68 per minute before, 74 per minute during, and 72 per minute after smoking. Of the four showing increase in peripheral blood flow when smoking, two had slight increases in rate and two were unchanged; the averages for the whole group were 63 per minute before, 68 per minute during, and 64 per minute after smoking (Table I).

The Effect of Smoking on Basal Metabolic Rate.—There were no significant changes in basal metabolic rate as a result of smoking. In the decreased

peripheral blood flow group the averages were +12 per cent before, +12 per cent during, and +13 per cent after smoking, although there were changes in individual patients. The averages for the increased peripheral blood flow group were 6 per cent before, 11 per cent during, and 11 per cent after smoking (Table I).

The Effect of Smoking on Average Skin Temperature.—In the group showing decrease in peripheral blood flow when smoking, the average skin temperature decreased in nine patients either during or after smoking and increased in four. The average for the group was 33.88° C. before, 33.81° C. during, and 34.19° C. after smoking. The averages for those showing increase in peripheral blood flow showed essentially the same trends, being 34.23° C. before, 34.12° C. during, and 34.28° C. after. The average skin temperatures of these patients were higher than in the other group. The average maximum fall in temperature of the hand after smoking was 0.20° C., both in the decreased and increased peripheral blood flow groups, and in the feet the average maximum change was 0.10° C. increase in the increased peripheral blood flow group and 0.40° C. decrease in the decreased peripheral blood flow group. There were wide fluctuations in the temperatures of the hands and feet (Table I). The hands and feet exhibited the most marked changes, and the other areas of the body did not show any significant trends in the changes which were observed.

Effect of Smoking on Rectal Temperatures.—In the decreased peripheral blood flow group the rectal temperature increased in nine patients as a result of smoking, was unchanged in three, and decreased slightly in one. The average for the group was 37.03° C. before, 37.06° C. during, and 37.10° C. after smoking. The rectal temperatures increased in all of the four patients showing increase in peripheral blood flow when smoking; the average was 37.15° C. before 37.21° C. during, and 37.19° C. after smoking (Table I).

DISCUSSION

The peripheral blood flow decreased, as a result of smoking regular cigarettes, in thirteen patients and increased in four patients. In these latter four patients, however, the peripheral blood flow decreased in one or more of the values recorded either during or after smoking. The patients participating in this study were all in the later decades of life, had evidence of vascular disease, and were those in whom the vascular system may presumably have lost some of its resilience. In some instances the maximum fall in peripheral blood flow was attained while smoking and in others it was lowest in the period after the subject stopped smoking. In the subjects in the younger age group studied by Evans and Stewart,¹ there were six subjects in whom the peripheral blood flow decreased during the smoking of standard cigarettes in a manner comparable to the thirteen subjects in the observations now being reported (Table I). The averages for this normal group were 88 c.c. per square meter of body surface per minute before, 50 c.c. per square meter of body surface per minute during, and 60 c.c. per square meter of body surface per minute after smoking. The percentage changes as a result of smoking were, therefore, slightly greater in the normal group (the average decrease occasioned by smoking was 38 per cent in the older decades and 43 per cent in the younger decades) and the average return to the control levels took place more slowly in the younger age group.

In this older age group, the decrease in peripheral blood flow was accompanied by a slight rise in rectal temperature and by a slight fall in skin tem-

TABLE I. EFFECT OF SMOKING CIGARETTES ON THE PERIPHERAL BLOOD FLOW, RECTAL AND SKIN TEMPERATURES, HEART RATE, AND BLOOD PRESSURE

CASE AGE (YRS.) HISTORY NO.	TIME WITH REF. EFFECT TO SMOK- ING	PERIPH- ERAL BLOOD FLOW (C.C./M. ² /MIN.)	AVER- AGE RECTAL TEMPER- ATURE ° C.	AVER- AGE WEIGHT ED SKIN TEMPER- ATURE ° C.	SKIN TEMPERATURES AT ELEVEN POINTS ON THE BODY SURFACE											BLOOD PRES- SURE MM. HG	PULSE RATE PER MIN.	BASAL META- BOLIC RATE PER CENT	DIAGNOSIS
					1 ° C.	2 ° C.	3 ° C.	4 ° C.	5 ° C.	6 ° C.	7 ° C.	8 ° C.	9 ° C.	10 ° C.	11 ° C.				

<i>Those in Whom Smoking Decreased the Peripheral Blood Flow</i>																			
N. H.	Before	53	37.58	34.16	35.3	34.9	34.4	34.2	34.4	34.7	35.2	33.8	32.9	33.3	33.6	107/65	75	- 8	Arteriosclerotic heart
53	During	13	37.60	34.40	35.6	35.2	34.8	34.8	34.5	34.4	35.0	34.6	33.0	33.3	33.6	118/80	93	+ 4	disease. Angina pec-
275880	After	52	37.74	34.32	35.4	35.2	34.9	34.9	35.0	34.4	34.6	34.6	33.3	32.7	32.7	111/69	85	+ 6	toris. Anemia
D. G.	Before	81	36.89	34.19	35.1	34.7	34.3	34.6	33.9	33.7	34.4	34.3	33.2	33.7	34.3	115/75	65	- 9	Arteriosclerotic heart
63	During	47	36.94	34.22	35.1	34.5	34.3	34.6	33.9	33.9	34.6	34.3	33.2	33.8	35.5	118/80	72	- 9	disease. Coronary
83994	After	56	36.99	34.43	35.1	34.6	34.5	34.9	34.5	34.2	34.1	34.5	33.5	33.9	34.6	116/76	66	- 9	thrombosis
M. K.	Before	114	36.94	33.44	34.7	34.7	33.7	33.8	33.8	33.8	33.8	32.3	32.4	32.1	32.0	120/79	63	+30	Arteriosclerotic heart
67	During	53	36.93	32.92	34.3	34.3	33.4	33.5	33.6	33.0	33.0	33.0	31.8	31.4	31.3	126/78	64	+34	disease. Coronary ar-
352240	After	63	36.92	33.18	34.6	34.4	33.9	33.8	33.8	33.6	33.8	33.2	31.8	31.5	31.3	125/75	62	+43	tery disease. En- larged heart
N. M.	Before	166	37.18	34.45	35.7	35.3	35.1	35.4	34.5	34.6	35.3	34.3	33.8	32.7	32.4	108/68	70	+37	History of fluctuation
38	During	136	37.28	34.34	35.7	35.5	34.8	35.1	34.7	34.6	34.3	34.4	33.7	32.6	32.6	118/74	84	+36	in blood pressure and
355327	After	130	37.29	34.39	35.6	35.5	34.7	35.2	34.6	34.6	34.8	34.9	33.6	32.7	32.3	127/81	84	+36	being high in last two years
F. S.	Before	56	37.32	34.54	35.5	35.6	35.3	35.2	34.9	34.3	34.9	34.5	32.4	33.6	34.0	148/90	72	- 5	Hypertensive heart dis-
54	During	36	37.35	34.51	35.5	35.6	35.3	35.3	34.6	34.3	35.0	34.3	32.8	33.5	33.9	155/94	76	- 5	ease. Angina pec-
342341	After	16	37.39	34.71	35.5	35.5	35.6	35.3	34.9	34.7	34.8	34.6	33.1	33.5	34.2	153/100	74	- 5	toris. Auricular fibrillation
F. C.	Before	79	36.78	34.10	34.4	34.7	34.3	34.0	34.2	33.7	34.8	33.7	33.9	33.1	33.1	152/98	73	+10	Hypertensive heart dis-
54	During	53	36.92	34.06	34.5	34.9	34.1	33.9	33.9	34.0	34.6	33.7	34.1	32.9	34.9	166/106	72	+11	ease. Enlarged
106423	After	95	36.96	33.95	34.3	34.3	34.0	33.7	33.9	33.9	34.4	33.4	34.1	33.1	33.1	156/106	74	+11	heart. Cerebral thrombosis. Arterio- sclerosis
P. L.	Before	79	37.40	33.71	34.0	34.8	33.8	34.6	33.7	33.0	34.5	33.2	33.1	32.3	34.1	197/103	83	+20	Hypertensive heart dis-
53	During	32	37.36	33.76	34.1	34.9	34.0	34.7	33.8	33.1	34.8	32.5	33.0	32.3	34.4	210/110	82	+19	ease. Coronary ar-
384879	After	71	37.39	33.89	34.1	35.0	34.3	34.7	34.0	33.1	34.8	32.7	33.2	32.5	34.5	208/106	81	+21	tery disease. Chronic pyelonephritis
H. S.	Before	87	37.30	33.80	35.1	35.4	34.8	34.9	34.3	33.4	34.2	33.1	33.0	31.8	31.4	176/87	72	+36	Hypertension. Arterio-
77	During	22	37.38	33.34	35.1	35.2	34.2	34.4	34.1	34.4	33.9	32.4	32.4	30.9	30.9	172/94	76	+30	sclerotic heart dis-
109660	After	39	37.42	33.70	35.2	35.4	34.6	34.8	34.2	33.8	34.3	33.1	33.2	31.0	31.4	176/90	73	+32	ease. Auricular fibrillation

H. S.	Before	84	36.40	53.48	34.6	34.0	33.4	33.2	32.9	34.5	32.4	33.3	32.9	33.8	107/64	62	- 0.4	Arteriosclerotic heart
70	During	59	36.41	33.73	34.4	34.5	33.9	33.6	33.4	35.0	32.8	33.4	33.1	34.5	115/70	68	- 0.4	disease. Coronary
61672	After	62	36.41	33.62	34.6	34.4	33.9	33.6	33.3	34.4	32.4	33.4	32.9	33.9	114/68	66	- 2	artery disease. En- gined pectoris, En- larged heart
A. K.	Before	62	36.70	33.79	34.4	34.3	33.9	34.2	33.3	34.8	34.0	32.8	32.9	33.8	127/61	56	+ 4	Arteriosclerotic heart
81	During	42	36.74	33.74	34.6	34.4	33.8	33.2	33.4	34.9	33.4	32.7	33.1	34.0	130/78	56	+ 3	disease. Coronary
230574	After	26	36.80	33.75	34.5	34.1	34.0	33.1	33.3	35.1	33.7	32.5	33.0	34.1	132/67	57	- 0.9	thrombosis. General- ized arteriosclerosis
V. B.	Before	49	36.89	33.43	33.8	34.3	34.1	33.6	34.4	34.4	32.6	32.8	31.3	33.1	108/68	53	- 7	Arteriosclerotic heart
54	During	35	36.88	33.28	34.7	34.9	34.1	34.4	33.9	33.8	32.8	32.3	30.6	32.6	112/75	58	- 8	disease. Coronary
364494	After	28	36.98	33.40	34.8	34.8	34.0	33.8	34.2	34.3	32.8	32.6	30.0	32.4	110/71	59	- 8	thrombosis
W. M.	Before	57	36.92	33.83	35.2	33.3	34.5	34.2	33.8	34.1	33.5	33.5	33.0	32.0	168/100	70	+15	Hypertensive and ar-
69	During	53	36.88	33.77	35.1	34.6	34.3	34.1	33.8	33.6	33.4	33.6	32.9	32.2	194/104	76	+12	teriosclerotic heart
212967	After	75	36.88	34.00	35.2	34.8	34.5	34.3	33.9	34.0	33.4	33.7	33.0	32.1	185/104	74	+13	disease. Enlarged
																		heart. Coronary ar-
																		tery disease
L. M.	Before	46	37.13	33.60	34.7	34.8	33.4	34.9	33.6	35.0	32.4	34.1	31.6	32.1	132/70	71	+36	Arteriosclerotic gan-
65	During	37	37.13	33.52	34.8	34.7	33.4	34.9	33.7	33.4	32.3	34.3	31.4	31.9	146/70	80	+33	grace of the right
255998	After	51	37.17	33.65	34.9	35.1	33.9	35.0	33.9	34.9	32.4	34.0	31.2	32.1	144/72	80	+33	foot. Experiment 41
																		days after amputa-
																		tion
Averages	Before	78	37.03	33.88	34.8	34.7	34.2	34.4	34.0	33.7	33.5	32.9	32.6	33.2	134/79	68	+12	
	During	48	37.06	33.81	34.9	34.9	34.2	34.4	33.9	33.8	33.4	32.9	32.4	33.3	145/86	74	+12	
	After	59	37.10	34.19	34.9	34.9	34.4	34.5	34.1	33.8	33.5	33.0	32.4	33.1	143/83	72	+13	
B. C.	Before	91	37.01	34.35	35.0	35.0	34.9	35.4	34.5	34.0	34.8	33.5	33.2	32.8	163/91	74	+23	Hypertension. Arterio-
69	During	102	37.02	34.30	35.1	35.0	35.3	35.6	34.4	33.6	34.6	33.4	33.1	32.1	170/90	72	+27	sclerotic heart dis-
377456	After	124	37.09	34.42	35.1	35.1	35.4	35.7	34.4	34.0	34.5	33.5	33.3	32.4	163/91	76	+25	ease
J. S.	Before	39	36.91	34.12	35.0	34.7	34.3	34.7	34.4	34.7	33.7	33.6	32.7	33.5	149/75	55	- 1	Arteriosclerotic heart
52	During	51	37.01	34.14	35.3	34.8	34.5	34.9	34.5	34.6	33.5	33.7	32.5	33.4	150/78	60	+ 7	disease. Enlarged
158786	After	37	37.06	34.24	35.2	35.2	34.7	34.8	34.6	34.6	33.2	33.6	32.6	33.8	149/76	59	+ 5	heart
J. S.	Before	21	37.46	33.86	35.0	34.4	34.2	34.4	34.0	33.9	33.5	32.6	32.6	33.4	211/126	62	+ 4	Hypertensive heart dis-
44	During	37	37.49	33.79	35.3	34.6	34.4	34.2	34.2	34.0	33.2	32.4	32.6	33.0	212/122	78	+ 4	ease. Coronary
353263	After	136	37.29	34.04	35.0	34.6	34.8	34.5	34.2	34.1	33.4	32.6	32.8	33.9	204/124	66	+ 7	thrombosis

Those in Whom Smoking Increased the Peripheral Blood Flow

TABLE I—CONT'D

CASE NO.	AGE (YR.)	TIME WITH REFERENCE TO SMOKEING	PERIPHERAL BLOOD FLOW (C.G./M. ² /MIN.)	AVR. AGE RECTAL TEMPERATURE °C.	AVR. AGE WEIGHT-PER MIN. TEMPERATURE °C.	SKIN TEMPERATURES AT ELEVEN POINTS ON THE BODY SURFACE											BLOOD PRESSURE MM. HG.	PULSE RATE PER MIN.	BASAL METABOLIC RATE PER CENT	DIAGNOSIS
						THE BODY SURFACE														
						1 °C.	2 °C.	3 °C.	4 °C.	5 °C.	6 °C.	7 °C.	8 °C.	9 °C.	10 °C.	11 °C.				
C. T.	52	Before	17	37.20	34.00	35.2	35.0	34.8	35.2	34.7	34.0	34.7	34.6	34.5	33.8	33.9	115/64	60	- 4	Arteriosclerotic heart disease. Enlarged heart. Auricular fibrillation. Pulmonary fibrosis.
	82	During	42	37.32	34.24	35.4	35.1	34.5	34.3	34.7	34.1	34.1	34.5	34.0	32.9	33.5	110/80	60	+ 5	
	355770	After	59	37.30	34.40	35.1	34.9	34.8	34.9	34.6	34.0	34.5	34.6	34.2	33.1	33.6	123/70	56	+ 6	
Averages		Before	50	37.15	34.23	35.1	34.8	34.6	34.9	34.4	34.2	34.7	34.2	33.6	33.1	33.4	160/89	63	+ 6	
		During	68	37.21	34.12	35.3	34.9	34.7	34.8	34.5	34.1	34.5	34.0	33.4	32.8	33.0	161/93	68	+11	
		After	89	37.19	34.28	35.1	35.0	34.9	35.0	34.5	34.2	34.7	33.9	33.5	33.0	33.4	160/90	64	+11	
Normal Subjects in Whom Smoking Decreased the Peripheral Blood Flow																				
F. H.	24	Before	77	36.78	33.87	34.2	34.0	34.0	34.1	34.1	33.9	34.6	33.6	33.7	33.3	33.5	112/67	56	- 3	
	69145	During	41	36.84	33.74	34.5	34.0	34.2	34.1	34.1	33.7	34.2	33.3	33.4	33.0	32.7	119/82	77	- 6	
		After	25	36.91	33.51	34.4	33.9	34.2	33.6	34.1	33.7	34.4	32.9	33.2	32.5	32.4	120/80	63	- 7	
R. B.	26	Before	39	37.10	33.41	34.9	34.2	34.4	34.7	33.7	33.7	33.8	33.9	33.0	33.2	26.3	105/69	60	+ 1	
	212215	During	10	37.14	33.79	34.8	34.8	35.1	35.2	34.3	34.1	34.1	34.1	34.3	33.5	25.2	122/81	86	0	
		After	52	37.11	33.71	34.8	34.6	34.7	34.9	34.0	34.1	34.2	34.2	33.8	33.5	25.7	117/77	76	0	
R. T.	28	Before	60	36.58	33.70	34.2	33.9	33.7	33.6	33.7	33.7	34.7	32.6	33.5	33.6	34.2	114/73	65	-19	
	64919	During	39	36.59	33.60	34.4	33.9	34.1	33.9	33.8	33.5	33.8	33.1	33.8	33.5	31.0	126/86	98	-15	
		After	65	36.53	33.61	34.3	33.9	34.0	33.8	33.6	33.7	34.3	33.1	33.8	33.4	31.6	120/79	72	-13	
W. B.	30	Before	71	36.95	34.18	34.7	35.4	35.1	35.1	34.0	33.5	34.7	33.8	33.2	34.0	30.6	97/65	64	- 1	
	235164	During	21	37.17	34.47	34.6	35.2	35.0	35.5	35.1	34.2	34.3	33.8	33.9	34.2	31.5	108/74	88	+ 5	
		After	50	37.28	34.70	34.8	35.5	35.3	35.4	35.1	34.4	34.6	34.3	34.2	34.4	31.8	103/65	75	+ 6	
E. B.	24	Before	119	37.02	34.21	34.5	34.5	34.0	34.4	34.1	34.0	35.0	33.7	34.1	34.0	34.3	104/74	71	+ 2	
		During	68	37.03	34.22	34.4	34.6	34.0	34.6	34.1	34.0	34.8	33.8	34.4	34.1	33.5	117/83	80	+ 5	
		After	76	37.13	34.43	34.4	34.9	34.5	34.7	34.2	34.3	35.0	33.9	34.6	34.1	31.0	107/73	71	+ 7	
G. V.	19	Before	163	36.26	34.12	34.4	34.8	34.4	34.4	34.3	34.2	34.3	33.2	34.1	33.5	33.7	99/65	52	- 6	
	39354	During	115	36.33	33.90	34.3	34.7	34.1	34.4	34.1	33.9	33.6	33.3	34.0	33.2	33.1	111/74	62	-11	
		After	105	36.36	33.88	34.2	34.9	34.2	34.2	34.4	33.8	33.8	33.1	33.9	33.1	32.9	103/69	57	-10	
Averages		Before	88	36.78	33.92	34.5	34.5	34.3	34.4	34.0	33.8	34.7	33.5	33.6	33.0	32.1	105/69	61	- 4	
		During	50	36.85	33.95	34.5	34.5	34.4	34.6	34.3	33.9	34.3	33.6	33.4	33.6	31.2	117/80	82	- 4	
		After	60	36.89	33.98	34.5	34.6	34.5	34.4	34.2	34.0	34.6	33.6	33.9	33.5	31.4	112/74	69	- 3	
Data from Evans and Stewart.																				

Data from Evans and Stewart.

perature with a fall in hand temperature. For the whole group there was, on the other hand, a rise in foot temperature and a rise in blood pressure and in pulse rate.

The decrease in peripheral blood flow with smoking is an expression of the arteriolar constriction which takes place. There is a decrease in skin temperature. As the body is unable to lose as much heat through the skin in which there is arteriolar constriction the rectal temperature rises. Another instance in which this occurs in the human body was shown clinically by Evans and Stewart⁶ in a patient who suffered from an adrenal pheochromocytoma. In this patient the peripheral blood flow was decreased, the rectal temperature was elevated, the skin was cold, and the heart rate was increased before operation when the patient exhibited an elevated blood pressure, even though there was marked elevation of basal metabolic rate. After removal of the tumor, the basal metabolic rate fell to normal, the peripheral blood flow increased, the rectal temperature fell, and the skin temperature rose.

When the changes resulting from smoking in these older persons are compared with the averages of six young individuals, the fall in peripheral blood flow, as we have already indicated, was slightly less (and in foot and hand temperatures was very much less) and the rise in blood pressure and pulse rate was less in the old age group. The effects of smoking standard cigarettes, therefore, in the older age group are essentially the same as in the younger normal age group, but they are quantitatively less.

The difference in magnitude of response to smoking in these older subjects may be due to the arterial system, in them being more rigid and less resilient than in the younger individuals. Alteration in response to stimuli with aging of the human organism is a common experience. For instance, it is well known that atropine increases the heart rate much less in an older individual than in a younger one. These changes, so far as the effects of smoking standard cigarettes are concerned, are the same as those found by Evans and Stewart¹ and Roth, McDonald, and Sheard³ in young normal subjects.

It has been shown in these observations that the smoking of two cigarettes not only brings about alterations in the peripheral blood flow, blood pressure, and heart rate, skin temperature, and rectal temperature, while the cigarettes are being smoked, but the effects may still be present as long as *thirty minutes* afterward. It is apparent that with repeated smoking at short intervals these effects of smoking may be more or less continuous and persistent throughout the smoking period of the twenty-four hours.

Clinically, there did not appear to be any characteristics to differentiate the four patients in whom smoking increased the peripheral blood flow. In them, moreover, there was no significant change in blood pressure or heart rate on smoking, further indicating a basic difference in response.

Since smoking cigarettes is now shown in the older age group as well as in young subjects to give rise to arteriolar constriction and certain other effects on the cardiovascular system, the data now being reported indicate that smoking may be harmful in certain peripheral vascular diseases in which the blood supply to the periphery is already decreased. Since smoking decreases the peripheral blood flow and decreases the skin temperature of the hands and feet it is not out of order to ask whether or not it is wise to allow wounded and "shocked" soldiers and sailors to smoke in spite of the "lift" which they derive from smoking.

SUMMARY

The effect of smoking standard cigarettes on the peripheral blood flow was studied by means of a method with which the average amount of blood allotted to the periphery can be measured in cubic centimeters per square meter of body surface per minute. The peripheral blood flow was measured in seventeen patients who exhibited evidences of hypertension and coronary arteriosclerosis and who were in the older age group ranging from 38 to 81 years of age. Effects on the basal metabolic rate, blood pressure, and pulse rate were also recorded. Studies were made before, during, and after the smoking of one brand of regular commercial cigarettes. All observations were made with patients in a basal metabolic state at a room temperature of 27° C. and 45 to 50 per cent humidity.

1. As a result of smoking, the peripheral blood flow decreased in thirteen subjects and increased in four subjects. In the four showing increases, the peripheral blood flow decreased for single observations either during or after smoking but not sufficiently to counterbalance the average trend of increase in peripheral blood flow for the whole period of the observations. After cessation of smoking the peripheral blood flow continued to decrease in some and began to return toward the control levels in others.

2. The blood pressure rose and the pulse rate increased in the group in which smoking decreased the peripheral blood flow, but it was essentially unchanged in the group in which smoking increased the peripheral blood flow.

3. The rectal temperature rose as a result of smoking.

4. The average skin temperature decreased as a result of smoking.

5. These changes resulting from smoking are similar to those occurring in normal subjects.

6. The changes in peripheral blood flow, blood pressure, heart rate, rectal temperature, and average skin temperature (especially the temperature of the hands and feet) were, however, less marked in these patients in the later decades of life than in normal young subjects.

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ELECTROCARDIOGRAPHIC CHANGES IN EARLY SYPHILIS PRIOR TO AND UPON COMPLETION OF INTENSIVE ARSENOTHERAPY

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IN SYPHILIS, the blood stream is invaded early in the infection, and it is generally admitted that, during this period, the treponemas lodge in the various viscera.¹ Yet many observers² deny the early invasion of the heart, except on rare occasions, and have held that cardiac syphilis is essentially a late manifestation, usually occurring fifteen to twenty-five years after the original infection. Wilson and his co-workers³ were convinced that reliable clinical evidence of electrocardiographic involvement of the heart or aorta during the primary and secondary stage must be exceedingly rare. Turner and White's¹ observations showed nothing conclusive to indicate changes in the heart muscle in the primary and secondary stages.

Our hospital unit had been receiving many untreated cases of early syphilis. In view of the conflicting opinions in the literature and also the lack of previous demonstrations of significant alterations in the electrocardiogram in early syphilis, it was considered opportune to investigate this problem. A report of our findings appears to be of interest.

METHOD AND PROCEDURE

Routine electrocardiograms were taken in one hundred consecutive cases of primary and secondary syphilis that were admitted to this general hospital for the twenty-day course of intensive arsenotherapy recommended at the time in this theater. Briefly outlined, the treatment consisted of the intravenous injection of 1 mg. Mapharsen per kilogram of body weight per day, the total dose not exceeding 75 mg. daily. The electrocardiograms were taken prior to, and upon completion of, the arsenotherapy. The conventional limb leads were obtained with the patient in a semirecumbent position, to exclude alterations attributable to changes in position. The galvanometer was standardized to a sensitivity of 1 cm. deflection per 1 millivolt. The patients were normal American soldiers who were admitted for untreated primary and secondary syphilis. The patients all received a complete medical examination before the commencement of therapy. Laboratory studies, in addition to the electrocardiogram, included a complete blood count, a platelet count, measurement of bleeding and coagulation time, urinalysis, determination of the sugar and nonprotein nitrogen, of the blood icterus index, intravenous hippuric acid function test, and examination of the spinal fluid. In the case histories given below, only the abnormal findings will be noted.

RESULTS

Four patients (4 per cent) of our series on admission showed definite alterations from the normal electrocardiogram. Following the twenty-day course of intensive arsenotherapy as previously outlined, the electrocardiograms in these cases had all become normal.

None of the patients with a negative quantitative Kahn test on admission showed any electrocardiographic changes, while four out of fifty patients (8 per cent) with primary and secondary syphilis and positive quantitative Kahn tests showed abnormal tracings. Two out of seven patients (29 per cent) with skin lesions of secondary syphilis and two out of ten patients (20 per cent) with a generalized lymphadenopathy had abnormal electrocardiographic findings.

The alterations were chiefly found in the final deflection. The T waves in four cases were abnormally low before treatment. In Lead I, the T waves were isoelectric in one case, almost isoelectric and slightly diphasic in another, and less than 0.5 mm. amplitude in every instance. In Lead II, the T waves were inverted in one case, isoelectric in another, and less than 0.5 mm. amplitude in every instance. In Lead III, the T waves were isoelectric or inverted in all the cases. Following the twenty-day course of arsenotherapy, the T waves increased in amplitude to normal levels in every instance (Figs. 1, 2, 3, and 4 inclusive).

There were at least six additional cases that showed definite increases in the amplitudes of the T waves following therapy; but, though the T waves were of low voltage prior to the therapy, the electrocardiograms were still within normal limits (Fig. 5).

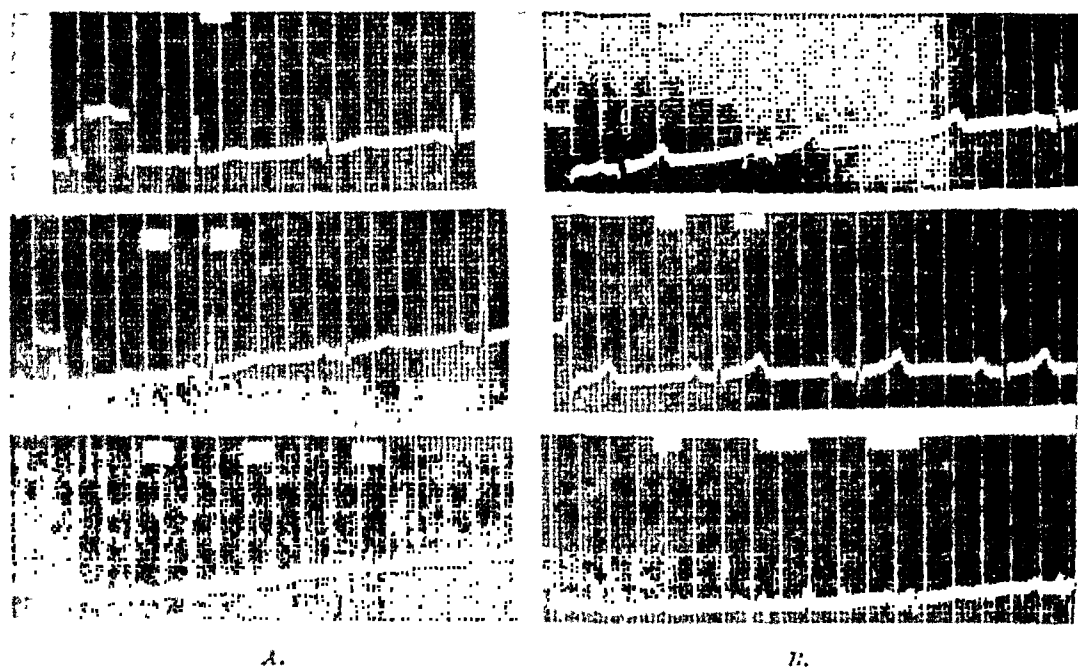


FIG. 1.—Case 1. A, Oct. 9, 1943, electrocardiogram prior to arsenotherapy showing abnormal T waves. B, Nov. 7, 1943, the T waves increased in amplitude following the twenty-day course of arsenotherapy.

Occasionally, there was low voltage of the initial complexes with some slurring, and the S-T segments were slightly depressed. In one instance, persistent ectopic ventricular extrasystoles were present; they disappeared only during the therapy. One case showed a shifting pacemaker which disappeared at the time of completed arsenotherapy.

In none of the cases was there evidence of any recent illness other than syphilis; nor was there any history of cardiovascular or allied diseases.

CASE REPORT

CASE 1.—A 29-year-old white man was admitted to the hospital with a history of a penile lesion of three weeks' duration and a generalized skin eruption of two days' duration. His health had always been excellent.

Physical examination revealed a well-developed young adult with a generalized maculosquamous skin eruption and a generalized shotty lymphadenopathy. There was a shallow ulcer on the shaft of the penis. The heart was of normal size and configuration; the heart sounds were of normal quality and the blood pressure was 128/78.

The quantitative blood Kahn test was positive in a titer of 160 units. An electrocardiogram taken prior to therapy showed a regular sinus rhythm of 66 per minute. The T waves were less than 0.5 mm. in amplitude in Leads I and II and slightly inverted in Lead III (Fig. 1, *A*). The second electrocardiogram, taken seven days after arsenotherapy, was completely normal (Fig. 1, *B*).

CASE 2.—A 23-year-old Negro was admitted to the hospital with a history of multiple penile lesions and a generalized skin rash of three weeks' duration. His health prior to this had always been excellent.

Physical examination revealed a thin, somewhat "anxious" young Negro. There were generalized discrete keratotic skin lesions, about 0.5 cm. in diameter, which were receding; lesions on the tongue, palate, and tonsils; condylomas on the scrotum; and shallow ulcers on the shaft of the penis. There was a generalized lymphadenopathy. The heart was of normal size and configuration and hyperactive to palpation. On auscultation, a transient soft systolic murmur was heard at the basal area with an accentuation of the second pulmonic sound. The blood pressure was 154 to 134/86.

The quantitative blood Kahn test was positive in a titer of 80 units. The first electrocardiogram taken prior to arsenotherapy showed a sinus tachycardia of 104 per minute. The T waves were almost flattened and slightly diphaseic in Lead I, less than 0.5 mm. in amplitude in Lead II, and inverted in Lead III (Fig. 2, *A*). Ten days following therapy, the electrocardiogram had become normal with T waves of normal amplitude (Fig. 2, *B*).

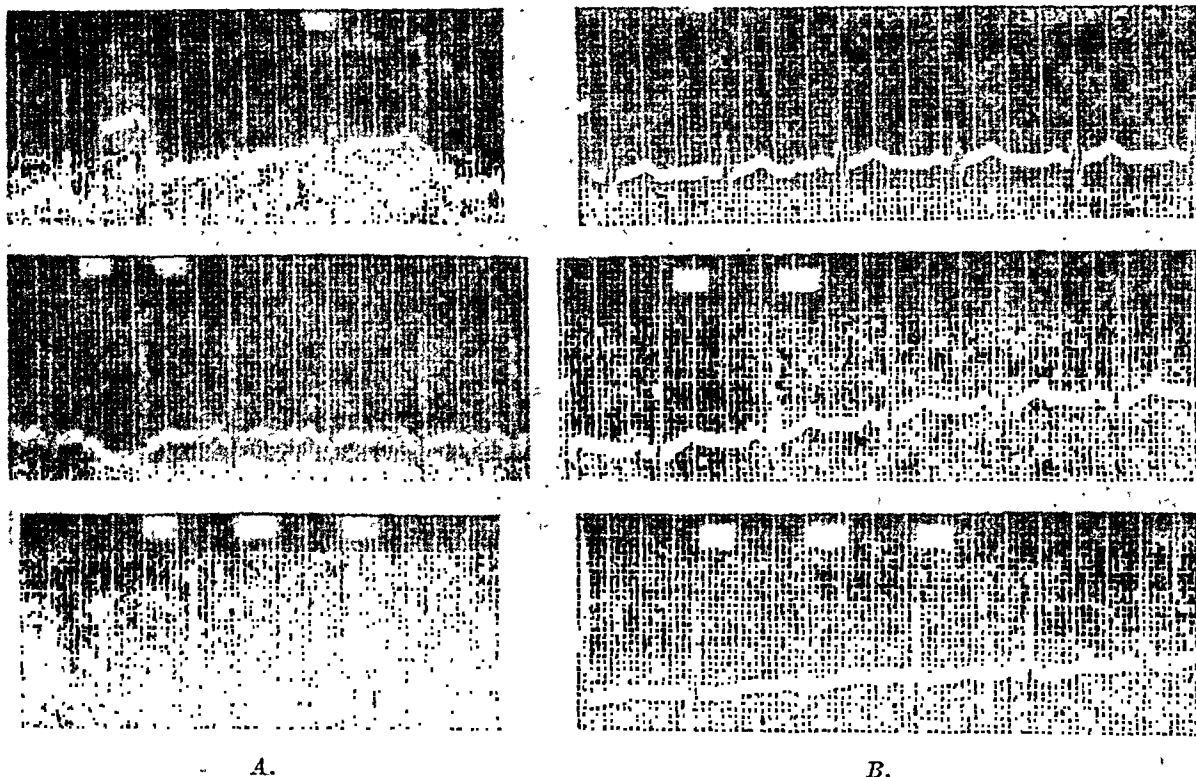


Fig. 2.—Case 2. *A*, Oct. 4, 1943, electrocardiogram prior to arsenotherapy showing abnormal T waves. *B*, Nov. 7, 1943, the T waves increased in amplitude following the twenty-day course of arsenotherapy.

CASE 3.—A 33-year-old Negro was admitted to the hospital with a history of a penile lesion of three weeks' duration. The past history was entirely negative.

Physical examination revealed a well-developed young adult resting comfortably. His heart was of normal size and configuration; the sounds were of normal quality, and the blood pressure was 134/80. There were two small ulcers on the penis.

The quantitative blood Kahn test was positive in a titer of 10 units. The first electrocardiogram showed regular sinus rhythm of 84 per minute. The T waves were 0.5 mm. amplitude in Lead I, isoelectric in Lead II, and slightly inverted in Lead III (Fig. 3, *A*). Ten days after completion of arsenotherapy, the electrocardiogram showed an increase in amplitude of the T waves to a normal height (Fig. 3, *B*).

CASE 3.—A 22-year-old Negro was admitted to the hospital with a history of a penile lesion of three months' duration and a persistent headache with moderate weakness of several days duration. His past history was not significant.

Physical examination revealed an adult Negro lying quietly, but uncomfortably, in bed. The heart was of normal size and configuration; the sounds were of normal quality, and the blood pressure was 120/86. Two shallow ulcers were present on the corona of the penis. A few discrete small nontender axillary and inguinal nodes were palpable. The deep reflexes were hyperactive but equal bilaterally. There was moderate nuchal resistance on flexion.

On admission, the quantitative blood Kahn test was positive in a titer of 80 units. The spinal fluid was clear with normal dynamics; there were 141 cells per cubic millimeter with

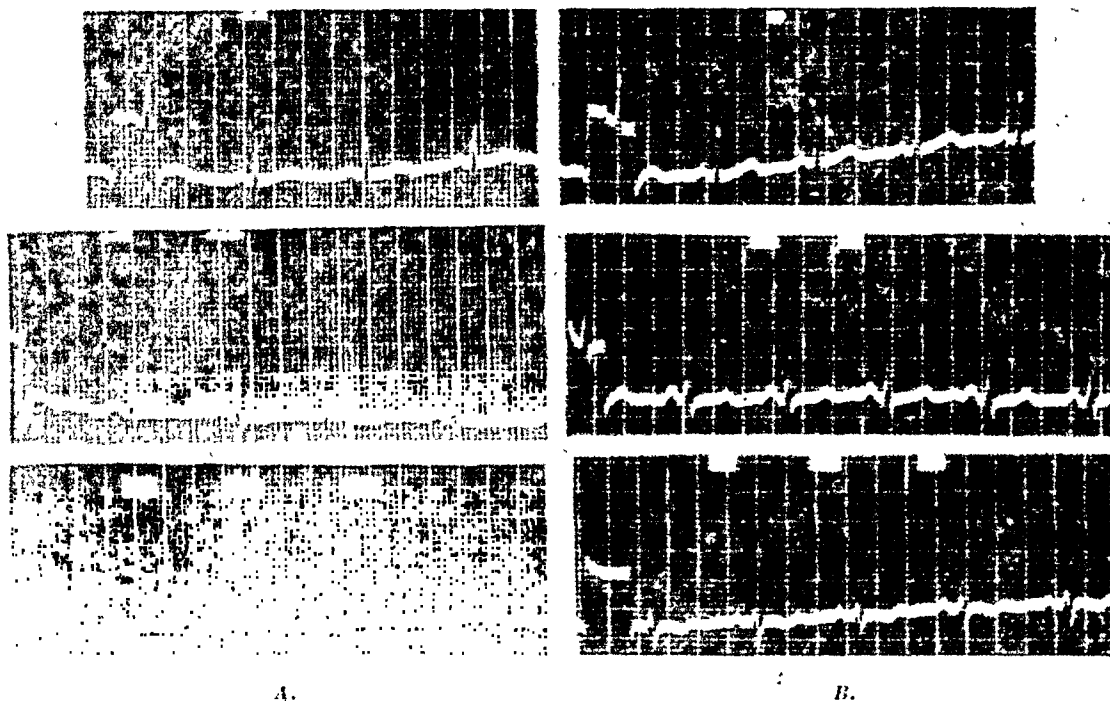


FIG. 3.—Case 3. A, Oct. 4, 1943, electrocardiogram prior to arsenotherapy, showing abnormal T waves. B, Nov. 4, 1943, the T waves increased in amplitude following the twenty-day course of arsenotherapy.

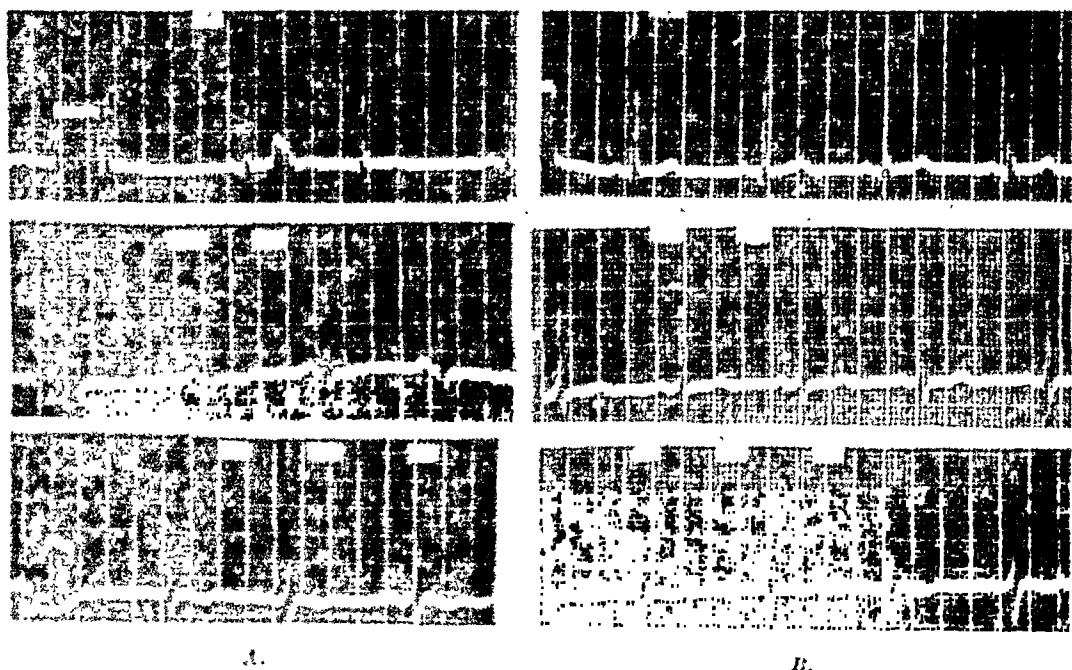


FIG. 4.—Case 4. A, Sept. 5, 1945, electrocardiogram prior to arsenotherapy showing abnormal T waves. B, Oct. 5, 1945, the T waves increased in amplitude following the twenty-day course of arsenotherapy.

31 polymorphonuclears and 110 lymphocytes; total proteins, 56.2 mg. per cent; sugar, 62.3 mg. per cent; Kahn test, negative; and colloidal gold curve, 0012332000.

The electrocardiogram taken prior to massive arsenotherapy showed a regular sinus rhythm of 60 per minute. The T waves were isoelectric in Lead I and inverted in Leads II and III (Fig. 4, A). The second electrocardiogram taken seven days after completion of the arsenotherapy showed a return to normal with positive T waves of 1.4 mm. amplitude in Lead I and 1 mm. amplitude in Lead II (Fig. 4, B).

It was also noted in this patient that, during the therapy, the spinal fluid findings returned to normal; the quantitative Kahn test became negative; and the patient was entirely asymptomatic upon discharge.

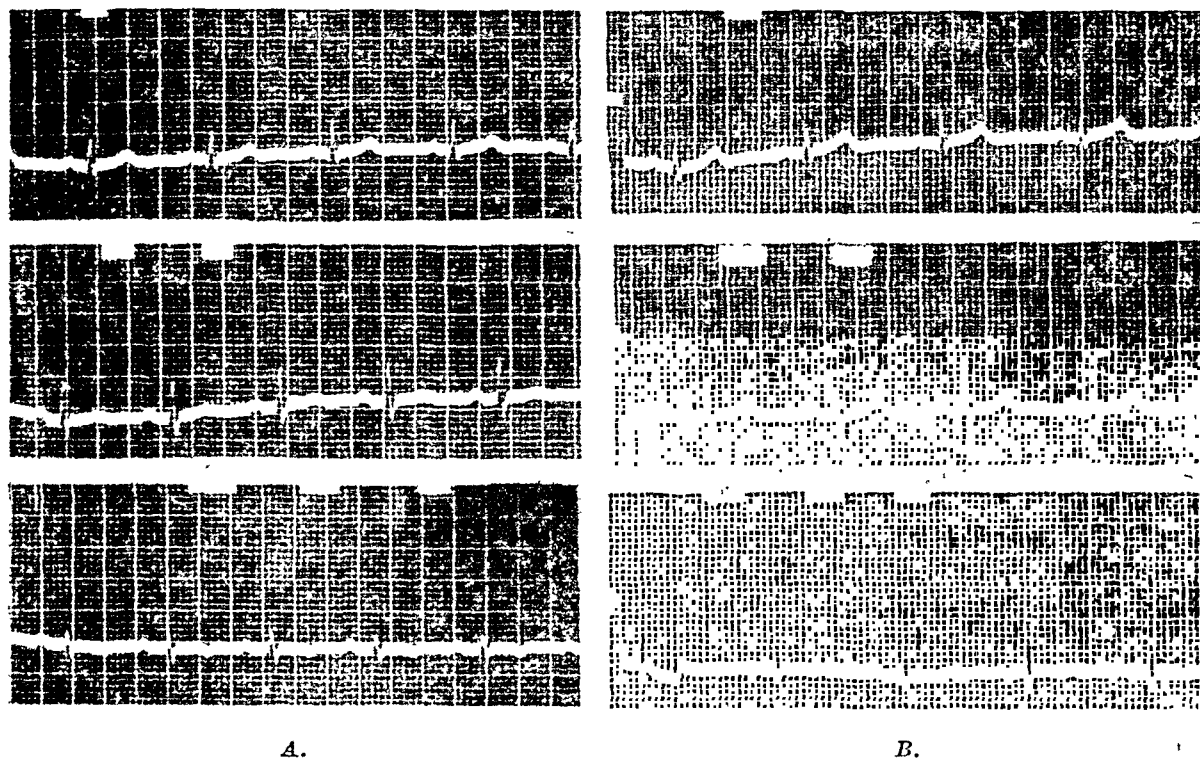


Fig. 5.—A, July 15, 1943, electrocardiogram prior to arsenotherapy showing low voltage T waves. B, Aug. 15, 1943, the T waves increased in amplitude following the twenty-day course of arsenotherapy.

DISCUSSION

There is a great divergence of opinion as to the frequency with which clinical, electrocardiographic, and radiologic evidence of involvement of the heart can be found in early syphilis. It seems to be the consensus among recent investigators that conventional forms of examination yield very little as ordinarily applied. Wilson and his co-workers (60 cases),³ Turner and White (50 cases),¹ Arnett (25 cases),⁴ and Ingraham and Maynard (27 cases),⁵ all had found no significant alterations in the electrocardiograms of primary and secondary syphilis.

Yet earlier workers found clinical symptoms and signs of early invasion of the heart and aorta. Brooks (1921),⁶ in a study of 300 cases of secondary syphilis, found clinical evidence of cardiac involvement in 8 per cent of the cases. Hermann⁵ discussed a case of pericarditis in a patient with a severe roseolar rash of acute syphilis which cleared promptly with intensive arsenotherapy. Stokes⁷ states, "There is every reason to believe, from what is known of the pathologic mechanism of the disease, that cardiovascular syphilis should be all but universal during the late primary and early eruptive stages of the infection." Warthin's work suggests that the myocardium is involved with great frequency as a blood stream infection, so that the invasion would be *a priori* in the secondary stage. It is established that spirochetes will invade the myocardium; this is evidenced by the ease with which they can be visualized in the myocardium in congenital syphilis.⁸

Coombs⁹ describes an acute vascular inflammation in the early stage, even before the skin rash appears, which is called an acute coronaritis. Pathologically, there are small blood vessel changes, localized perivascular or more diffuse myocardial mononuclear cell infiltrations.

Master¹⁰ observed six cases of syphilis with low voltage T waves. Unfortunately, there is no information given as to whether they were early or late cases of syphilis. One of the patients, aged 37 years, with syphilis of the larynx and bones and a 4-plus Wassermann test, received antisyphilitic therapy for one and one-half years. Following this, the Wassermann test was negative and a repeated electrocardiogram showed an increase in the amplitude of the T waves in Leads I and II. Master felt the flat T wave in these cases may have been due to a syphilitic involvement of the myocardium. One of us (Klotz) has observed a patient with syphilis of the bones whose electrocardiogram showed flat T waves. After six months of iodide therapy, there was marked clinical and radiological evidence of improvement in the bony involvement and the electrocardiogram showed an increase in the amplitude of the T waves.

In their observations of electrocardiographic changes in 23 cases of early syphilis following the five-day massive arsenotherapy (240 mg. Mapharsen daily) Geiger and his co-workers¹¹ were concerned mainly with the diminution, disappearance, or reversal of the original upright T-wave deflection during the therapy with subsequent return to normal levels within a few weeks. These changes occurred to a lesser degree with the twenty-day arsenotherapy regime in about 10 per cent of our series. However, it was noted that the T waves in many of their cases subsequently returned to levels higher than were present in the tracings taken prior to the onset of the therapy.

It is difficult to explain the absence of demonstrable electrocardiographic changes in the series of recent investigators. All our patients were soldiers on foreign duty who were received untreated, directly from their units. It was noted, in the series of Turner and White,¹ that all the patients had received at least three arsenic injections before the studies were made. Stokes,⁷ in his discussion of the early detection of meningeal involvement, states, "It is important to realize that the age of the infection and the amount of treatment given the patient before the first spinal fluid examination will markedly influence the percentage of abnormality found." Perhaps this should also be applied to the detection of early electrocardiographic changes. In one of our cases (Case 4), the patient had evidence of early meningeal involvement in addition to the electrocardiographic changes; both became normal at the conclusion of the arsenotherapy.

It is probable that the T-wave changes observed in our cases are indicative of myocardial disturbances secondary to the syphilitic infection. That they reverted to normal so quickly with therapy is not unusual as similar observations have been made in other acute infections and deficiency states. In all our patients with early syphilis who have been treated with the twenty-day intensive arsenotherapy method the secondary lesions of the mucous membranes and skin usually healed within three to five days and always at the conclusion of the course of therapy. Since at this stage of the disease, the pathologic lesions are uniform in type, it is felt that the heart has healed in a similar manner.

SUMMARY

1. In a consecutive series of one hundred cases of primary and secondary syphilis, four cases were presented showing abnormal T waves in the electrocardiograms. These became completely normal following a twenty-day course

of arsenotherapy. Six additional cases showed low voltage T waves, which increased in amplitude at the completion of the arsenotherapy.

2. Other findings noted in isolated instances were low voltage with some slurring of the initial complexes, slight depression of the S-T segments, persistent ectopic ventricular extrasystoles, and a shifting pacemaker, all of which disappeared upon completion of the arsenotherapy.

3. It is felt that the electrocardiographic changes observed are indicative of myocardial disturbances in early syphilis which recovered following intensive arsenotherapy.

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STUDIES CONCERNING THE ETIOLOGY AND PATHOGENESIS OF NEUROCIRCULATORY ASTHENIA

IV. THE RESPIRATORY MANIFESTATIONS OF NEUROCIRCULATORY ASTHENIA

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ALTHOUGH the patient suffering from neurocirculatory asthenia (NCA) experiences various symptoms, those which appear to arise from dysfunction of the respiratory system incapacitate him most severely. The patient with NCA can endure excessive perspiration, hyperthermia,¹ occasional or frequent episodes of giddiness,² tremor, the sharp transient type of precordial pain,³ and nervousness, but he seemingly is overwhelmed whenever tachypnea and dyspnea are part of the syndrome. And, unfortunately, easily induced tachypnea and dyspnea occur in over 90 per cent of patients with NCA.^{7, 12} Furthermore, it has been found³ that the tachypnea occurring in the patient with NCA is responsible in many instances for the tachycardia which also may arise in conjunction with the former manifestation of the syndrome. Wood¹² has pre-

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sented evidence, too, that suggests that the dull, persistent type of precordial pain frequently experienced by these patients is due to respiratory malfunction.

The exact causes for the respiratory distress of these patients are still unknown. Several investigators^{6, 10} have suggested that the entire syndrome of neurocirculatory asthenia with all of its manifestations, might be one of hyperventilation, but this suggestion has been discarded by more recent investigators.^{5, 11, 12} It was also suggested that the respiratory symptoms were due to cardiac dysfunction, but, in a previous study,³ we were unable to detect any basic cardiovascular abnormality in patients with this syndrome.

Because of the importance of the respiratory system in neurocirculatory asthenia, studies were made of fifty-four of the sixty patients with NCA of our series, who complained of dyspnea. In these studies, an effort was made to determine (1) the nature and cause of the tachypnea and dyspnea and (2) the pathogenesis of the dull, prolonged type of precordial pain so frequently complained of. The results of these studies follow.

THE NATURE AND CAUSE OF THE TACHYPNEA AND DYSPNEA

A. The Organic Status of the Lungs.—Clinical surveys, teleroentgenograms, sedimentation rates, and multiple examinations of sputa for the tubercle bacillus were performed on each of the fifty-four patients with NCA studied. No evidence of active or chronic disease was found by these diagnostic measures in a single one.

Measurements of the vital capacity were obtained from fifteen patients who complained of experiencing severe dyspnea on slight exertion. It was found that their average vital capacity was 4,400 c.c., or 2.3 liters per square meter, which, according to the standards of Gross,⁴ represented a value within normal limits. Thus it would appear certain that not only were the lungs of the patient with NCA free of disease, but they were also normal in ability to take in and expel sufficient quantities of air.

B. The Capacity for Holding the Breath.—In both organic pulmonary and cardiac disease of a degree severe enough to produce dyspnea, the breathholding time is also reduced and both processes seem to be dependent on the same etiological factors. Likewise in the patient with NCA subject to dyspnea, it has been observed^{6, 12} that the breathholding time is reduced. In our series of patients with NCA, complaining of dyspnea on slight exertion, the average breathholding time was found to be 40 seconds (range: 25 to 60 seconds) which, when compared to the average breathholding time of 58 seconds (Range: 35 to 100 seconds), found in thirty normal individuals, represented a moderate but definite decrease. Furthermore, the breathholding time was found to be directly related to the severity of the dyspnea suffered, because in eleven patients subject to severe breathlessness on the slightest exertion, the average breathholding time was found to be even further reduced (average: 32 seconds). It seemed most likely, then, that the same mechanism underlying the dyspnea in the patient with NCA was also responsible for the diminution in duration of breathholding. Accordingly, the factors underlying the decrease in time of breathholding were investigated.

C. The Relation of Oxygen Excess to the Breathholding Capacity.—Five patients with NCA, complaining of severe dyspnea on slight exertion, and five normal persons were allowed to breathe pure oxygen for three minutes. At the end of this time, they were instructed to hold their breath as long as possible. It was found that the average breathholding time of the five patients

with NCA was 32 seconds before, and 34 seconds after, the respiration of oxygen. However, the breathholding time of the five normal subjects was 60 seconds before, and 90 seconds after, the same procedure. Thus, the normal person gained approximately 50 per cent in breathholding time, whereas no appreciable gain occurred in the patient with NCA. This suggested that the decrease in breathholding time (and, by inference, the dyspnea also) of the patients with NCA was not due to oxygen lack because they were not benefited by an excess of it.

D. The Relation of Oxygen Lack to Tachypnea and Dyspnea.—The same five patients with NCA and the five normal persons previously described, were then given pure nitrogen to breathe by mask, after basal respiratory and pulse rates had been obtained. They were instructed to signal with the right hand when they first experienced unendurable dyspnea. As Table I indicates, the patients with NCA, despite the fact that they were breathing no oxygen, exhibited no greater increase in respiratory or pulse rate than did the normal individual. Of even greater importance, they did not experience more rapidly occurring dyspnea than did the normal individuals, although they were deeply cyanotic fully thirty seconds before they signalled the onset of unbearable dyspnea. These observations indicated conclusively that neither the tachypnea nor the dyspnea of the patient with NCA was dependent on an oxygen deficiency, either in the blood or in the tissues, because it was obvious that as long as these patients were allowed to go through the sheer, but oxygen-profitless, mechanics of breathing, neither objective nor subjective differences in cardiorespiratory dynamics were observed between them and the normal subjects.

TABLE I. THE TIME OF ONSET OF DYSPNEA IN PATIENTS WITH NCA AND IN THE NORMAL PERSONS DURING THE INHALATION OF PURE NITROGEN

CASE	BREATH-HOLDING, MAXIMUM (SEC.)	BEFORE NITROGEN INHALATION		DURING NITROGEN INHALATION		
		RESPIRATORY RATE (PER MIN.)	PULSE RATE (PER MIN.)	TIME OF ONSET OF UNENDURABLE DYSPNEA (SEC.)	RESPIRATORY RATE (PER MIN.) AT END	PULSE RATE (PER MIN.) AT END
<i>Patients With NCA</i>						
28	25	20	82	210	26	122
42	32	18	80	195	28	120
45	30	20	84	220	28	124
46	28	18	84	165	32	130
50	45	20	78	240	30	126
Average	32	19	82	206	29	124
<i>Normal Persons</i>						
C-1	55	18	76	180	30	130
C-2	60	18	84	200	28	122
C-3	75	20	86	220	28	134
C-4	50	18	74	210	32	122
C-5	55	18	82	218	26	118
Average	59	18	80	205	29	125

E. The Relation of Carbon Dioxide Excess to Breathholding Capacity.—Although it was found that the diminution in breathholding and the occurrence of dyspnea in the patient with NCA were probably not due to a deficiency in oxygen supply, the possibility remained that these abnormalities in respiration were due to an abnormal increase in the blood gas, carbon dioxide. Accordingly, five patients with NCA and three normal persons were instructed to hyperventilate for seventy-five seconds (rate of respiration: 50 per minute) after

TABLE II. THE EFFECT OF HYPERVENTILATION ON THE BREATHHOLDING ABILITY OF PATIENTS WITH NCA AND OF NORMAL PERSONS

CASE	BEFORE HYPERVENTILATION		IMMEDIATELY AFTER HYPERVENTILATION	
	BREATHHOLDING MAXIMUM (SEC.)	CO ₂ COMBINING POWER-PLASMA (VOL.%)	BREATHHOLDING MAXIMUM (SEC.)	CO ₂ COMBINING POWER-PLASMA (VOL.%)
<i>Patients With NCA</i>				
30	40	55	15	46
42	35	62	15	56
47	40	56	26	50
55	35	50	28	45
Average	38	56	21	49
<i>Normal Persons</i>				
C-2	60	56	88	46
C-3	75	54	86	48
C-4	50	54	80	48
Average	62	55	85	47

control determinations had been taken of their breathholding capacity and the carbon dioxide combining power of venous blood. Immediately after the cessation of hyperventilation, a second determination of breathholding and of the carbon dioxide combining power of the venous blood was obtained. As Table II shows, although in both the normal person and in the patient with NCA, the blood carbon dioxide concentration was approximately equal and fell after hyperventilation by equal amounts, the breathholding ability of the patient was not only abnormally curtailed before hyperventilation, but failed to improve even after hyperventilation. These observations thus indicated that the decrease in breathholding time and, presumably also the dyspnea of the patient with NCA, were phenomena which were not due to an excess of carbon dioxide in the blood.

F. The Respiration During Effort.—Although it had been noted many times in the past that the respiratory and pulse rate of the patient with NCA might increase inordinately during effort, the observations strongly suggested that the tachypnea and dyspnea during effort were not due either to abnormalities in concentration of oxygen or to carbon dioxide in the blood. Since it was also found previously⁷ that the cardiac abnormalities occurring in the patient with NCA during effort were conceivably initiated by the respiratory dysfunction, it seemed quite likely that the respiratory dysfunction was neurogenic or psychogenic in origin.

In order to study this possibility, a group of six patients with NCA, complaining of severe dyspnea on slight exertion, and six normal young adults were allowed to perform a test previously described⁷ without preliminary introduction or orientation. It was observed (Table III) that the respiratory and pulse rates of the patients with NCA increased markedly and abnormally in comparison with those of normal persons. For example, the average respiratory and pulse rates in the patients with NCA, after only thirty seconds of performing the test, was 27 and 118 per minute, respectively, whereas it was 20 and 89 per minute, respectively, in the normal young adults. However, when the same groups performed the test after two practice trials (during which the test was discontinued approximately ten seconds after it was begun), it was observed (Table III) that the respiratory and pulse rates of the patients with NCA did not increase any more than did those of the normal persons taking the test. This improvement in the cardiorespiratory dynamics of the patient with NCA could not have been due to increased muscular efficiency in performing the test because

TABLE III. THE RESPIRATORY AND PULSE RATES OF PATIENTS WITH NCA AND NORMAL PERSONS DURING A SPECIAL EXERCISE TEST (BEFORE AND AFTER ORIENTATION)

CASE	BEFORE EXERCISE		DURING EXERCISE					
			AFTER 30 SECONDS OF EXERCISE		AFTER 60 SECONDS OF EXERCISE		AFTER 120 SECONDS OF EXERCISE	
	RESPIRATORY RATE (PER MIN.)	PULSE RATE (PER MIN.)	RESPIRATORY RATE (PER MIN.)	PULSE RATE (PER MIN.)	RESPIRATORY RATE (PER MIN.)	PULSE RATE (PER MIN.)	RESPIRATORY RATE (PER MIN.)	PULSE RATE (PER MIN.)
Before Orientation								
A. Patients With NCA								
21	20	80	24	100	28	110	30	120
23	18	88	24	120	30	124	32	122
24	22	92	28	124	32	122	34	128
25	20	82	32	128	34	130	32	136
26	22	88	28	116	26	124	28	130
27	18	82	24	120	28	128	30	134
Average	20	85	27	118	30	123	31	128
B. Normal Persons								
C-1	18	78	20	96	22	96	24	90
C-2	21	78	20	94	24	104	24	104
C-3	19	80	22	90	22	98	24	102
C-4	16	72	18	76	20	84	20	84
C-5	22	78	20	80	24	86	22	90
C-6	21	84	22	96	22	96	24	96
Average	20	78	20	89	22	94	23	94
After Orientation								
A. Patients With NCA								
21	20	76	20	86	24	98	26	96
23	18	82	18	94	20	100	24	100
24	18	80	20	90	20	98	22	100
25	20	72	22	86	24	98	26	98
26	20	86	18	88	20	94	22	98
27	18	80	20	88	22	96	22	96
Average	19	79	20	89	22	97	24	98
B. Normal Persons								
C-1	20	82	20	88	24	98	22	98
C-2	18	70	20	84	22	88	24	96
C-3	18	64	22	78	20	88	22	92
C-4	20	78	20	78	22	84	24	98
C-5	18	88	20	90	24	98	24	108
C-6	18	92	18	88	22	94	26	98
Average	19	79	20	84	22	91	24	98

their preliminary, orienting trials were too brief to allow such enhancement. Also, if sheer practice were the reason for their improvement, one would expect the normal adults to have shown a comparable improvement also, but, as Table III shows, they performed the test as well the first time as they did after the preliminary trials. It appears quite likely from these experiments that when some psychogenic or neurogenic element was eliminated by preliminary orientation, the previously observed, early, abrupt tachypnea and its accelerating effect on the pulse rate³ was eliminated in the patient with NCA taking the test.

G. *The Respiration at Rest.*—Although the basic respiratory rate of the fifty-four patients with NCA at rest in bed was found to be exactly similar to that of normal persons; fourteen of the patients with NCA (26 per cent) were subject to dramatically sudden, inexplicable attacks of tachypnea and dyspnea which were associated with manifestations of a generalized sympathetic discharge and the *facial representation, but not the conscious realization, of anxiety.* When these episodes of spontaneous respiratory dysfunction were considered

with the previously described evidence that the respiratory dysfunction was not dependent on basic abnormalities in the lung, the heart, or on the concentration or exchange of blood gases, it became obvious to us that the fundamental disturbance underlying the respiratory difficulties of the patient with NCA, both at rest and during effort, was either a psychogenic or neurogenic one.

THE PATHOGENESIS OF THE DULL TYPE OF PRECORDIAL PAIN

A. Clinical Characteristics of the Dull Type of Precordial Pain.—In a previous article,³ two types of precordial pain were distinguished as occurring either separately or together in the patient with NCA. In the same study, it was observed that one of these types, the sharp, transient pain, was found to be associated and apparently arising from actual, but temporary, cardiac dysfunction. The etiology, however, of the second type of pain (the dull, prolonged pain of the left chest with maximal intensity around the left nipple) was found to be, as Wood¹² suggested, of respiratory origin. Twenty-seven patients of our series (45 per cent) gave a history of experiencing this latter type of pain. Twelve of these patients also experienced the sharp, transient type, at times, but they were able to differentiate the two forms quite readily.

The onset of dull precordial pain was almost always preceded, either immediately or considerably earlier, by indulgence in vigorous exertion during which excessive tachypnea and tachycardia had occurred. The sensation of pain was described as "aching" or "sore" but never as sharp or lancinating in character. Its duration varied from ten minutes to many hours. Only five of the twenty-seven patients exhibited tenderness over the precordial area. It was observed further that, when suffering from this pain, the patient with NCA, without exception, avoided lying on the left side, for this position accentuated the intensity and duration of the symptom. Characteristically the pain was not aggravated by a single deep inspiration.

B. The Type of Respiration Exhibited With Dull Precordial Pain.—As Wood¹² pointed out, we also have observed that patients with NCA, subject to attacks of dull precordial pain, almost invariably used only the upper third of the chest in breathing. When the twenty-seven patients experiencing episodes of dull precordial pain were compared with twenty-three patients with NCA who did not experience this pain, and with ten normal individuals, it was found (Table VI) that, whereas twenty-four of the twenty-seven patients subject to attacks of pain, breathed exclusively, at rest, with the upper third of the chest, only four of the twenty-three patients not subject to attacks of pain breathed in this fashion. None of the normal subjects were observed to breathe in this fashion.

Similarly, it was found (Table IV) that the average maximal expansion of the upper third of the chest of the patient with NCA, having attacks of pain, was greater than the maximal expansion of the lower third (6.1 cm. compared with 5.8 cm.). This finding was in sharp contrast with the measurements of the chest expansion in the patient with NCA not subject to pain and with those of the normal individual. In the patient without pain, maximal expansion was in the lower third of the chest whereas in the normal individual, the average maximal expansion of the lower third of the chest was 3.4 cm. greater than that observed in the upper third (Table IV).

These observations made it clear that the patient who experienced attacks of dull, precordial pain, breathed in a different fashion than both the patient without pain and the normal person. Furthermore, the marked change in the

TABLE IV. THE RESPIRATORY CHARACTERISTICS OF PATIENTS WITH NCA, SUBJECT TO DULL PRECORDIAL PAIN, OF PATIENTS WITH NCA, NOT SUBJECT TO DULL PRECORDIAL PAIN, AND OF NORMAL PERSONS

CASE	TYPE OF RESPIRATION	UPPER CHEST EXPANSION, MAXIMUM (CM.)	LOWER CHEST EXPANSION, MAXIMUM (CM.)	EXPIRATORY PRESSURE, MAXIMUM (MM. HG)
<i>A. Patients With NCA Subject to Dull Precordial Pain</i>				
1	Thoracic	—	—	46
2	Thoracic	6	7	75
3	Thoracic	—	—	55
5	Thoracic	5	6	—
7	Thoracic	8	8	—
9	Thoracic	5	5	74
16	Thoracic	7.5	9	64
20	Thoracic	4	2.5	46
21	Abdominothoracic	8.5	8	38
23	Thoracic	—	—	46
24	Thoracic	6	8	38
25	Thoracic	10	9	65
26	Thoracic	5	3	45
28	Thoracic	4	4.5	46
29	Thoracic	7	8.5	44
32	Thoracic	5	7	74
36	Abdominothoracic	4	2.5	84
37	Thoracic	—	—	66
39	Thoracic	8	6	60
40	Thoracic	4	4	70
41	Thoracic	6	5	52
42	Thoracic	7	9	46
44	Abdominothoracic	3.5	2	70
45	Thoracic	9	5	74
49	Thoracic	7	4.5	68
56	Thoracic	3	3	32
62	Thoracic	7	6	42
Average		6.1	5.8	57
<i>B. Patients With NCA Not Subject to Dull Precordial Pain</i>				
8	Abdominal	7	9	70
11	Abdominal	—	—	90
13	Abdominal	4	5	110
14	Abdominal	4.5	5	98
17	Abdominal	6.5	8	68
18	Thoracic	4	4	78
19	Abdominal	7	9	120
22	Abdominal	4	6	90
27	Abdominal	5	4	88
30	Abdominothoracic	6	11	65
31	Thoracic	—	—	100
33	Abdominal	—	—	70
34	Abdominothoracic	4	6	100
35	Abdominothoracic	—	—	75
38	Thoracic	8	6	45
43	Abdominothoracic	9	14	—
47	Abdominal	9	12	80
48	Thoracic	7	9	65
51	Abdominal	4.5	9	88
60	Abdominal	—	—	96
61	Abdominal	6.5	8.5	110
63	Abdominal	9	9.5	84
64	Abdominal	5.5	8.5	94
Average		6.1	7.9	86
<i>C. Normal Persons</i>				
C-1	Abdominal	6	10	100
C-2	Abdominal	6	9	116
C-3	Abdominal	9	10	120
C-4	Abdominal	2	6	100
C-5	Abdominal	4	9	—
C-6	Abdominal	4	5.5	140
C-7	Abdominal	5	11	118
C-8	Abdominal	9	11	122
C-9	Abdominal	3	7	—
C-10	Abdominal	6	9	126
Average		5.4	8.8	118

normal pattern of regional, maximal expansion of the chest in the patient subject to attacks of pain suggested that his peculiar type of upper chest respiration was probably of long standing. As a matter of fact, when these patients were asked to breathe in the lower chest or abdominal fashion, it was noticed that many of them were totally incapable of doing so, so fixed had their pattern of upper-chest breathing become.

Five patients with dull pain were observed fluoroscopically and the suspicion gained from clinical examination was confirmed: during quiet respiration, the diaphragm did not move significantly. This inadequacy of diaphragmatic movement was even more clearly suggested when the maximal expiratory pressure of the patient with attacks of pain was measured. It was found (Table IV) that the average maximal expiratory pressure of twenty-five patients with NCA, experiencing precordial pain, was 57 mm. Hg, whereas the average maximal pressure was 86 mm. Hg in twenty-two patients with NCA not subject to pain, and 118 mm. Hg in eight normal persons. It was possible, of course, that this striking decrease in the expiratory pressure of the patients subject to precordial pain was due to some generalized weakness of the total respiratory musculature, but this seemed unlikely in view of the fact that these patients were fully as robust as those not subject to pain. In view of the type of upper-chest respiration, and the observed inertia of the diaphragm, it seemed most likely that the impairment of expiratory pressure in the patient with NCA subject to pain was due to the lack of efficient or total diaphragmatic participation in the process of expiration.

C. The Production and Abolition of Dull Precordial Pain in Patients With NCA.—The preceding observations demonstrated that the patient with NCA, subject to attacks of precordial pain, breathed in a different manner than either the patient not subject to pain or the normal person. These studies did not prove, however, that the pain was caused by this difference in mode of respiration. Likewise, the abolition of dull precordial pain by anesthetization of the intercostal musculature in the precordial area, as reported by Wood¹² cannot be construed as unequivocal proof that this pain arose because of upper-chest breathing. Nevertheless, these observations were quite suggestive and if, in addition, it were found that the pain could be provoked or intensified in susceptible patients by experimental accentuation of upper-chest breathing, and diminished or abolished in these patients by experimental inhibition of upper-chest breathing, the evidence would be quite conclusive for the assumption that the dull type of precordial pain was caused by the method of respiration.

Accordingly, fifteen patients with NCA, subject to frequent attacks of dull precordial pain following very slight exertion, and five normal young adults were asked to breathe deeply and rapidly for two minutes at a rate of 40 respirations per minute. At the end of this time, they were asked only how they felt, while no specific reference was made to the possible presence of precordial pain. Each of the patients complained of dizziness, and nine complained of dull precordial pain which they stated was identical with that which they previously had experienced following exercise. The normal persons had no symptoms other than slight lightheadedness.

In another experiment, eight patients with NCA, subject to frequent and seemingly spontaneous attacks of dull precordial pain lasting from twenty minutes to several hours during each day, were instructed to expire all possible air from the lungs. Adhesive tape was then applied to the entire chest, down to the level of the eighth rib, in such a manner that upper-chest breathing was markedly

reduced; this forced them to resort to lower-chest and abdominal breathing. This adhesive-tape restraint was left on the patients for six days, and, during the last four days of this period, none of the patients experienced any attacks of pain. When the adhesive tape was removed, however, it was observed that all of the patients reverted immediately to their previous method of upper chest respiration, and within a period of twenty-four hours, all of them again began to experience attacks of dull, precordial pain.

D. The Production of Dull Precordial Pain in Normal Young Adults.—Fifteen normal young adults who never had experienced precordial pain were selected for this experiment. They were directed to indulge in strenuous exertion of a standard type for three days (trotting 600 yards on three separate occasions during an afternoon). After this control period, the chests of five of these subjects were splinted with adhesive tape as described previously. In the remaining ten subjects, however, the chest was bound with adhesive tape in such a manner that the lower third of the chest and the upper half of the abdomen were immobilized, so that they were forced to breathe almost exclusively with the upper half of the chest. The fifteen subjects were then instructed to engage again in the same exercise (daily) which they previously had taken. Although none of them had noticed any symptoms during the control period, it was noted that considerable tachypnea and dyspnea occurred in the ten subjects forced to breathe predominantly with their upper chest, whenever they indulged in the standard exercise. Eight of the ten subjects whose lower chest was immobilized, began to complain, on the second day of the experiment, of dull, aching precordial pain which came on about an hour after the performance of the last exercise of the afternoon. On the third day of the experiment, nine of the ten subjects, who were forced to breathe with the upper chest, complained of precordial pain. The adhesive tape restraints were removed from all on the fourth day, but the exercises were continued. Following the removal of the adhesive tape, the subjects previously experiencing precordial pain after exercise, became symptomless. At no time during the experiment, did any of the five adults whose upper chest was splinted, complain of precordial pain.

DISCUSSION AND SUMMARY

Evidence was obtained in the preceding studies that the tachypnea, dyspnea, and diminution in breathholding, so frequently found in the patient with NCA, were respiratory dysfunctions which were not caused by either disease or organic abnormality of the lung. It was also found that these functional respiratory abnormalities were not caused by any quantitative peculiarity of the blood gases or by defective utilization of these same gases by the tissues. In a previous study³ it was discovered that the respiratory disturbances did not arise from cardiac dysfunction but, as a matter of fact, the disturbances in respiration influenced the cardiodynamics. On the other hand, the normality of the respiratory processes in patients with NCA while performing an exercise test (which, prior to mental or emotional orientation, they performed only with considerable tachypnea and dyspnea), strongly suggested that, when respiratory abnormalities did occur in these patients, they were not initiated by any organic or functional defect in the cardiorespiratory system. Finally, our observation of the spontaneous occurrence of sudden, inexplicable attacks of tachypnea and dyspnea accompanied by manifestations of sympathetic discharge in many patients with NCA, at rest in bed, indicated conclusively that the respiratory difficulties encountered in neurocirculatory asthenia are of psychogenic or neurogenic origin.

The dull type of precordial pain so frequently found in the syndrome of neurocirculatory asthenia was discovered to result from the method of respiration employed by the susceptible patient, a method in which the diaphragm was minimally, and the intercostal musculature maximally, utilized. The experimental production and abolition of precordial pain in both the susceptible patient with NCA and the normal person, by the employment of measures altering the manner of respiration, further indicated the pathogenesis of this manifestation of neurocirculatory asthenia. The localization of this pain in the precordial area of the chest was considered to result from the traumatic effect of the contracting heart on this portion of the intercostal musculature, as suggested by Wood.¹²

In previous articles,¹⁻³ evidence was presented which suggested that hypothalamic dysfunction was the mediating agent in the clinical emergence of *somatic manifestations of neurocirculatory asthenia*. In the present study, any correlation of the respiratory manifestations of the syndrome with hypothalamic dysfunction is difficult to prove. It is well known,^{8, 9} however, that hypothalamic dysfunction may lead to respiratory abnormalities. It should be mentioned also that the spontaneous attacks of tachypnea and dyspnea associated with sympathetic manifestations of anxiety (without conscious experience of emotion on the part of the patient), which was observed by us in the patients with NCA at rest in bed, could be considered as strikingly similar to the behavior of the experimental animal whose hypothalamus had been stimulated, as described by Ranson.⁸

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CARDIAC ANEURYSM WITH SPONTANEOUS RUPTURE

REPORT OF TWO CASES

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A VENTRICULAR aneurysm of the heart, ominous in nature and seemingly a portent of danger because of its thin, scarred wall, seldom causes death by virtue of spontaneous rupture.¹⁻³ The usual terminal event is either slowly progressive cardiac failure or a cerebral embolus originating from a mural thrombus within the aneurysm.¹

Cardiac ventricular aneurysms may develop from various diseases of the heart. The most common lesion, comprising 85 per cent of the cases, is myocardial infarction following atherosclerotic occlusion of a coronary artery. The small percentage that remains develops secondarily to syphilitic myocarditis, rheumatic necrosis of the myocardium, myocardial abscesses from infective endocarditis, congenital defects, and trauma.^{2, 4, 5}

The development of a cardiac aneurysm following myocardial infarction is not a rare complication. A survey of 7,200 autopsies performed at the Pennsylvania Hospital reveals that death was caused by myocardial infarction, subsequent to atheromatous changes of the coronary arteries, in 141 cases. Such lesions as so-called "myocarditis" and rheumatic, syphilitic, and embolic changes are not included in this study. Cardiac ventricular aneurysm occurred in eleven of these 141 cases of myocardial infarction, giving an incidence of 8 per cent. Parkinson and his co-workers² concluded from the published post-mortem statistics of six separate groups of observers that cardiac aneurysm occurred in 9 per cent of similar cases. In our series of 7,200 successive autopsies, cardiac aneurysm developed in 1.5 per 1,000 cases. Lucke and Rea,⁶ in a comparable survey of 12,000 autopsies, found an incidence of 1.1 per 1,000.

Spontaneous rupture occurred in two of our eleven cases of cardiac aneurysm (18 per cent). Thurnam⁷ (1836) and Hall⁸ (1903) reported a spontaneous rupture incidence of 10 per cent and 15 per cent, respectively. In light of the relative infrequency of spontaneous rupture of cardiac ventricular aneurysm, it seems justifiable to report in detail the two following cases.

REPORT OF CASES*

CASE 1 (History No. 68294).—*First Admission*: J. M., a 62-year-old Puerto Rican male "kitchen worker," entered the hospital on May 30, 1944, with a chief complaint of pain in the anterior part of the chest of thirty-six hours' duration. Except for recent tiredness, weakness, and intermittent pain in the anterior part of the chest, he had been in his usual good health. Thirty-six hours before admission, he experienced a sudden severe pain over the whole anterior part of the chest; the pain radiated to the left scapula, and was associated with a cold sweat. One episode of vomiting relieved the pain slightly; however, the precordial pain continued in moderate degree until the time of entry. His past history was not contributory. He had had no exertional dyspnea, orthopnea, ankle edema, or cough.

Physical examination revealed a well-developed and well-nourished elderly man in no acute distress. The temperature was 98° F.; the pulse rate, 100 per minute; and the

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respiratory rate, 24. The blood pressure was 140/80. The heart was markedly enlarged to the left, the rhythm was regular, the cardiac sounds were of poor quality, and no murmurs were heard. The lungs were clear to percussion and auscultation. The abdomen and extremities were not remarkable.

The leucocyte count was 16,800 per cubic millimeter; the erythrocyte count was 4,100,000; and the hemoglobin was 15 Gm. An x-ray film of the chest showed a markedly enlarged heart to the left and posteriorly. The lung fields were not remarkable. An electrocardiogram, taken on May 31, 1944, approximately twelve hours after admission, revealed a low amplitude of T₁ and widened ventricular complexes. A second tracing, taken on June 5, 1944, showed a shortening of the ventricular complexes and elevation of the ST segment in Leads II, III, and IVF. These changes were interpreted as indicating "active myocardial pathology, most likely due to a recent myocardial infarct."

The patient was kept in bed for five weeks. His temperature was of the low-grade, intermittent type for the first two weeks, with gradual return to normal. He was discharged in an improved condition on July 6, 1944.

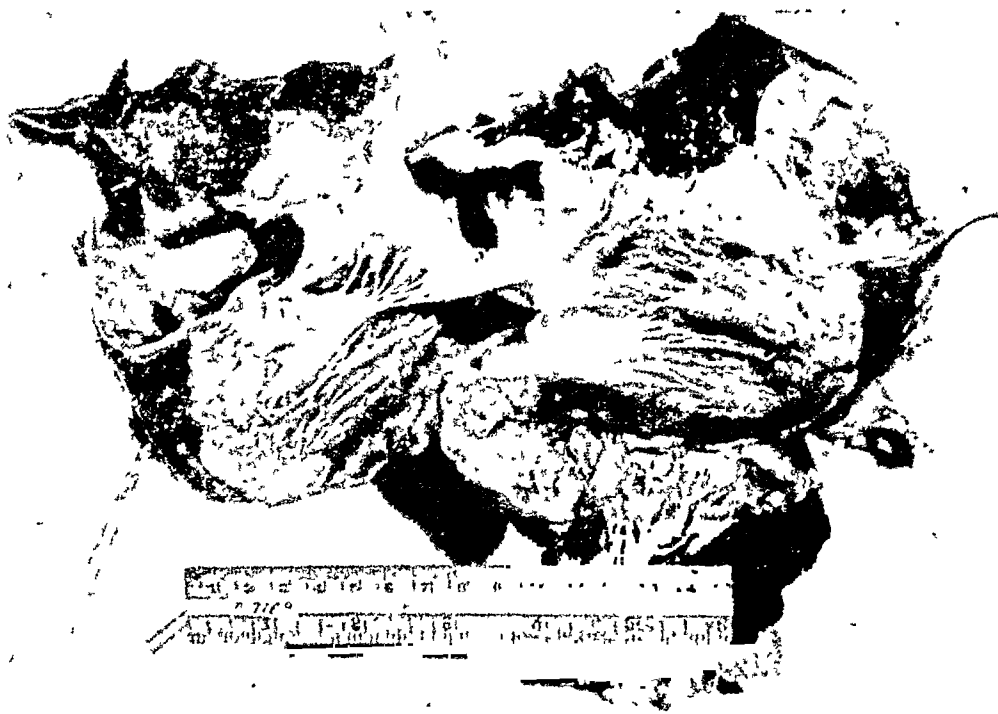


Fig. 1.—Sectioned aneurysm of the posterior wall of the left ventricle with rupture (arrow) Note the extensive hemopericardium.

Second Admission: He remained asymptomatic until the day of re entry, Oct. 9, 1944, when a severe substernal pain awoke him, and he found himself drenched with cold perspiration. He vomited several times.

Physical examination revealed an acutely ill man with slight cyanosis. His temperature was subnormal; the pulse rate was 120 per minute but very weak, and the respiratory rate was 32. The blood pressure was 50, systolic; the diastolic was unobtainable. There was no venous congestion of the neck. The cardiac sounds were very feeble, no murmurs were heard, and there were no precordial pulsations. There were a few moist râles at the bases of the lungs.

An electrocardiogram taken a few hours after arrival revealed slight right axis deviation and diphasic T₁ and T₂ "suggestive of a developing posterior myocardial infarct."

During the patient's hospitalization, the blood pressure never rose above 66/54. About forty hours after entry, as he lay slightly dyspneic and cyanotic in an oxygen tent, he suddenly had a generalized convulsion; he screamed as if in agonizing pain and died immediately.

*Post-Mortem Findings** (A. 7169): Thoracic cavity: The left pleural cavity was filled with 2,500 c.c. of blood which had compressed the left lung. The right pleural cavity contained 650 c.c. of cloudy straw-colored fluid. The heart was slightly displaced to the right.

*Unessential pathologic findings in this and the next case are omitted.

Heart (gross): The heart was greatly enlarged. The striking feature was the large aneurysmal sac projecting from the posterior wall of the left ventricle in the region of the septum (Fig. 1). This aneurysm measured approximately 10 cm. in diameter and had a 4 cm. orifice near the interventricular septum. It was filled with fresh blood as well as some organized clot at the periphery. The wall of the sac was extremely thin in places and was partially adherent to the pericardium. There was little or no muscular tissue in its wall. The aneurysm had ruptured into the pericardial space through a ragged tear about 1.5 cm. in diameter, and from there it broke into the left pleural cavity. Elsewhere the wall of the left ventricle was somewhat thickened, measuring 20 mm. in diameter. The left ventricle was a little compressed by the hemopericardium. The chamber of the right ventricle was greatly compressed by the encircling blood in the pericardial space. The valves were not particularly remarkable. The coronary vessels were slightly tortuous. There were a few areas of sclerosis, although no definite point of complete obstruction was found. Apparently the changes in the coronary vessels responsible for the aneurysm were in the circumflex branch.



Fig. 2.—Aneurysm of the anterior wall of the left ventricle involving the apex with rupture (arrow).

Heart (microscopic): Sections through the aneurysmal wall revealed an extensive scarring of the myocardium with degeneration of many of the myocardial cells, as well as hypertrophy and hyalinization of the fibrous tissue. The myocardium from areas near the sac showed a slight degree of fatty infiltration and became more scarred as one approached the aneurysmal wall. In the sac wall proper, there was complete obliteration of the muscle fibers. The pericardium was adherent to the epicardium and blended with it over the aneurysm. However, the pericardium and epicardium were separated at the periphery of the aneurysm by an organizing blood clot. The wall of the aneurysm was composed of a dense hyalinized union of endocardium, scarred myocardium, epicardium, and pericardium. The coronary vessels showed atherosclerosis, and the arterioles were markedly narrowed.

CASE 2 (History No. 58149).—D. O'B., a 52-year-old male laborer, walked into the Accident Ward of the hospital on March 21, 1941, complaining of chest pain. A few minutes after arrival, before he could be examined, he suddenly died. He had been seen in 1939 for a "traumatized hand," and again in 1940 for a "dermatitis of the left arm." There were no cardiac complaints during these visits.

Post-Mortem Findings (A. 6617): Thoracic cavity: There were 700 c.c. of clear straw-colored fluid in the left pleural cavity, and 100 c.c. on the right. The heart was in its normal position.

Heart (gross): The pericardium was distended by 700 c.c. of blood. The apex of the heart was fastened to the pericardium by old, fibrous adhesions except at its very tip. After opening the pericardium, a large aneurysm of the anterior wall of the left ventricle involving the apex was revealed (Fig. 2). This aneurysmal sac did not communicate with the ventricular cavity by means of a narrow neck but rather with its entire diameter. The wall of the aneurysm was thin, being composed of epicardium, a slight amount of necrotic myocardium, and endocardium. The sac measured 6.5 cm. in diameter. The myocardium about the aneurysm was soft, gray, and necrotic. There was a tear 3 cm. long at the apex of the aneurysm. The right side of the heart was not abnormal. There were no valvular lesions. The ostia of the coronary arteries were normally wide. On gross section of the coronary arteries, there was moderate arteriosclerosis throughout their course, but there was little calcification of the intima. No absolute obstruction of the coronary lumina was found. However, about 2 cm. distal to the origin of the anterior descending branch, there was an area of very marked narrowing.

Heart (microscopic): In sections of the aneurysmal wall near the apex, there were large areas of comparatively fresh uniform necrosis of the myocardium. However, fibroblasts and capillaries were already beginning to organize this necrotic tissue. Granulation tissue that was replacing muscle fibers was also proliferating on the epicardial surface of other areas of the anterior wall of the left ventricle. A varying amount of subacute inflammatory exudate was present in the epicardium. In a section of myocardium from the base of the left ventricle, there was diffuse hypertrophy of the muscle fibers and perivascular scarring. The myocardium of the right ventricle was not remarkable. The lumen of the anterior descending branch of the left coronary artery near the apex was markedly distorted by large intimal fatty and calcified plaques, but no complete obstruction was seen. There was also an area of fresh conglutination necrosis in its intima.

DISCUSSION

The original account of cardiac ventricular aneurysm seems to have been made by Galeati⁹ in 1757. Subsequent to this, numerous observers postulated various theories pertaining to the causes and development of this lesion. However, it was not until a century later that the present concept of pathogenesis was crystallized.¹⁰ We now know that, following an occlusion of a coronary artery, the myocardium becomes necrotic. In time, the muscle fibers are replaced by connective tissue. If, during this process, the affected area is not strong enough to withstand the intraventricular pressure, then a gradual bulging of the ventricular wall takes place. The resulting aneurysm may be saccular, having a small orifice; more commonly, it may be a large bulge that is not sharply demarcated from the ventricular cavity. The aneurysmal wall is usually very thin, being composed mostly of dense, firm, fibrous tissue. It may or may not contain a few muscle fibers and deposits of calcium. A mural thrombus is often present.^{1, 2, 5, 10, 11}

Of course, the relative age of the aneurysm when rupture occurs will determine the composition of the aneurysmal wall at the time of death. If the rupture is delayed, giving the aneurysm ample time to develop, then it will have a wall of well-organized connective tissue. Muscle fibers will be practically extinct. An example of this is seen in the first case. On the other hand, if the rupture occurs while the aneurysm is developing from an area of fresh myocardial infarction, then the wall of the aneurysm at time of death will be com-

posed largely of necrotic muscle cells with little fibrous tissue and organization. This is seen in the second case. The pathologic process in the two cases is the same. The only difference lies in the stage of development reached when rupture occurs.

The time that the infarcted myocardium gives way to aneurysmal dilatation has not been determined. It seems logical that aneurysmal development occurs during the period of myocardial necrosis and softening, which is most marked during the first two weeks after the coronary occlusion.¹ The fact that the degree of myocardial softening is a predisposing factor in spontaneous cardiac rupture following myocardial infarction substantiates this view.¹² It is further supported by the experiments of Sutton and Davis¹³ who showed in dogs that aneurysmal development was less likely to take place if the rest period after myocardial infarction was extended during the phase of myocardial softening.

A cardiac ventricular aneurysm usually involves the anterior wall of the left ventricle, often including the apex, simply because the anterior descending branch of the left coronary artery is most commonly occluded. In spite of the fact that the posterior wall of the left ventricle is frequently infarcted, aneurysm here is relatively rare. An aneurysm of the right ventricle occurs least of all.^{2, 4, 5, 10}

The clinician's interest in cardiac ventricular aneurysm is at present centered on ante-mortem diagnosis. Its symptomatology and physical signs have been extensively described.^{1, 2, 4, 10, 14} The significant features in this regard are: (a) a history of a previous coronary occlusion; (b) failure to observe the approved period of rest in bed after a myocardial infarction; (c) a forceful and diffuse cardiac thrust, being most marked within or outside the midclavicular line, usually at the level of the fifth rib; and (d) a very weak and feeble first sound at the apex. The blood pressure, murmurs, and a gallop rhythm are unreliable guides. The physical signs are dependent upon the location of the aneurysm, and are most commonly found if the lesion is at the apex.

Radiological examination has become the most important aid in diagnosis. However, a cardiac aneurysm may be present and yet give no x-ray evidence.¹¹ To avoid oversight, roentgenograms should be made in the anteroposterior and oblique positions and checked by fluoroscopy.¹⁵ If the lesion is at the apex, it may often escape detection because in this position the silhouette may appear merely as an elongation of the apical portion of the heart, or the lesion may be buried in the diaphragm.^{2, 14} A sharply defined, localized bulge and a paradoxical pulsation, i.e., expansion of the sac during systole and a decrease in its size during diastole, are pathognomonic.^{11, 16}

The role of the electrocardiogram as an aid in diagnosis of cardiac ventricular aneurysm has been claimed by Fulton¹ to be "of importance only as it may add to the evidence of myocardial infarction and assist in localizing the lesion in the anterior or posterior part of the ventricle." A similar opinion is also held by Parkinson and co-workers,² Dressler and Pfeiffer,¹⁴ and Sigler and Schneider.¹⁵ On the contrary, Eliaser and Konigsberg¹⁷ confirmed Nordenfelt's¹⁸ findings that the electrocardiogram may be of considerable diagnostic value. They believe that one of two types of electrocardiographic syndromes is present in 63.7 per cent of cases of aneurysm of the left ventricle following coronary occlusion. They feel that these syndromes are presumptive signs of the lesion, and when found should stimulate further diagnostic investigation. One type has "a downward directed major deflection in Lead I, with inversion of the

T wave and an upright P wave. The ventricular complex in Lead III is upright." The other type presents "ventricular complexes directed downward in Leads II and III with an upright major deflection in Lead I that may or may not be of low amplitude."

Cardiac ventricular aneurysm does not hold an immediate hopeless prognosis as is commonly thought. This lesion has quite a variable course, for the patient is always subject to repeated coronary occlusion, development of congestive failure, embolism, or rupture. Yet, ventricular aneurysm is not infrequently compatible with one or two years of moderately active life.^{1, 2, 4}

SUMMARY

1. Cardiac ventricular aneurysm is not a rare complication of myocardial infarction. Yet, it seldom causes death by virtue of spontaneous rupture.

2. Atherosclerotic coronary occlusion is responsible for 85 per cent of the cases of cardiac aneurysm.

3. Two cases of cardiac ventricular aneurysm that terminated in rupture are herewith presented.

4. The etiology, incidence, pathogenesis, site, prerequisites for ante-mortem diagnosis, prognosis, and course of this lesion are briefly presented. The roles of x-ray and electrocardiography are discussed.

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THE RELATIVE INCIDENCE OF RHEUMATIC VALVE DISEASE IN NEW YORK AND COSTA RICA AND ITS BEARING ON THE RHEUMATIC ORIGIN OF CALCAREOUS AORTIC STENOSIS

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STENOSIS of the aortic valve occurring in conjunction with deformities of other valves is generally believed to be rheumatic in origin. When it occurs without associated lesions of other valves, the etiology is less apparent. The three major opinions that have been expressed about the origin of this second group are (1) that the lesion is invariably the end result of rheumatic endocarditis;¹⁻⁸ (2) that it is primarily noninflammatory and the end result of a degenerative process analogous to sclerotic processes that occur in other parts of the vascular system;⁹⁻¹² and (3) that the lesion is sometimes the result of rheumatic disease and sometimes the result of degeneration followed by calcification.¹³⁻²⁰

The chief reasons for supporting the theory of the rheumatic origin of this form of valvular disease are as follows. A history of rheumatic fever earlier in life can be obtained in a significant number of cases (Christian¹ and Cabot²¹). Secondly, the lesion itself does not differ in appearance in any striking detail from that known to be the result of rheumatic infection, for example, in those cases in which the mitral valve is also deformed.^{7, 8, 21} Finally, evidences of rheumatic inflammation are sometimes found in the diseased valve itself or in other parts of the heart on histologic study.⁵⁻⁸

There are, however, a number of formidable objections that have been raised to dispute the view that rheumatism is the invariable cause of aortic stenosis. Acute rheumatic endocarditis limited to the aortic valve is seen much less often than is stenosis of that valve alone for example.²² Most series of cases reported show a striking preponderance of stenosis of the aortic valve in males,^{11, 12, 17, 18, 21} whereas all the other known types of rheumatic lesions occur about equally in both sexes. Calcareous aortic stenosis is seen in a much older age group than are the proved forms of rheumatic disease.²¹ Finally, mild degrees of calcification of the base of the aortic valve without deformity occur frequently in older age groups, particularly in males. Calcareous aortic stenosis has been interpreted as an extension of this process in certain susceptible individuals with advancing age. There are thus several reasons for accepting or denying each of the three opinions that have been expressed concerning the genesis of this lesion.

The incidence of rheumatic heart disease is believed to vary in different parts of the world and in different racial and economic groups. If this is so, it is possible to use this variation to obtain evidence as to whether or not calcareous aortic stenosis is always the result of rheumatic fever. In necropsy

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statistics that show a high incidence of rheumatic heart disease, the incidence of calcareous aortic stenosis should be correspondingly high. Conversely, if in a series of necropsies, the incidence of proved types of rheumatic heart disease is low, then calcareous aortic stenosis should also be infrequent. Deviations in the relative incidence of these lesions would suggest that rheumatic disease does not play an important role in the development of calcareous aortic stenosis.

The present report is an attempt to elicit information along these lines by comparing the incidence of rheumatic heart disease and calcareous aortic stenosis in three independent necropsy series using identical methods of analysis. The analysis was made on (1) 4,860 consecutive autopsies performed at Bellevue Hospital in New York City, (2) 5,700 consecutive autopsies performed at Long Island College Hospital and the Long Island College of Medicine division of Kings County Hospital in Brooklyn, New York, and, (3) 4,900 consecutive autopsies performed at the Hospital San Juan de Dios in San José, Costa Rica.

The sex and age distribution by decades was recorded for the entire group in each series. Each included a large, but variable, number of stillbirths and infantile deaths. There was a lesser number of childhood deaths. In the Long Island series 30.2 per cent of the autopsies were done on individuals less than 10 years of age, while in the Bellevue series only 10.1 per cent fell into this age period. Since rheumatic heart disease does not usually develop in infancy or early childhood, inclusion of this age group would make any comparison of rheumatic heart disease between the different hospital series inaccurate. The groups of persons who died before they reached the age of 10 years are, therefore, excluded from the tabulations. With these groups omitted, the Bellevue series is reduced to 4,370 of which 3,134 (71.7 per cent) were males, and 1,236 (28.3 per cent) were females. The Long Island series is reduced to 3,976 of which 2,361 (59.4 per cent) were males, and 1,615 (40.6 per cent) were females. Similarly, the Costa Rican series becomes 4,209 with 2,618 (59 per cent) males and 1,691 (41 per cent) females.

Cases included in the rheumatic group were those in which there was stenosis, insufficiency, or verrucous endocarditis of the mitral valve alone, or of both the mitral and aortic valves. In some of these the valves on the right side of the heart also had lesions. There were no examples, however, in any of the series of right-sided valve involvement without concomitant damage to the mitral and aortic valves. These cases are therefore not listed in separate categories. Cases of bacterial endocarditis were included only if pre-existing rheumatic damage to the mitral valve was demonstrable. The instances in which only the aortic valve was damaged are included in a separate category. Cases of syphilitic lesions of the aorta involving the aortic valves are excluded as are those cases in which the aortic valve was calcified at its attachment but in which the valves appeared to be competent. The results are recorded in Table I. It may be seen that among the cases of definite rheumatic lesions, i.e., those in which the mitral valve is damaged, there are certain features that are consistent for all three series and a few that are variable.

The consistent findings are the following. First, in each of the three series, mitral stenosis is more common in women than in men. Second, relatively the same proportion of mild and acute to stenotic lesions is seen in each of the three series. Third, when the incidence of each type of rheumatic valvular lesion is compared in each of the three series, the Long Island groups are found to be consistently higher than the corresponding groups in the other two. The

TABLE I. THE INCIDENCE OF VALVULAR LESIONS IN THREE AUTOPSY SERIES

VALVE INVOLVED	AUTOPSY SERIES*	ACUTE OR MILD LESIONS						STENOTIC LESIONS					
		MALE		FEMALE		TOTAL		MALE		FEMALE		TOTAL	
		NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
Group 1: mitral damaged; aortic normal	L. I.	30	(1.27)	54	(3.34)	84	(2.11)	20	(0.85)	65	(4.02)	85	(2.14)
	B. H.	34	(1.09)	9	(0.73)	43	(0.98)	21	(0.67)	32	(2.59)	53	(1.21)
	C. R.	13	(0.52)	28	(1.66)	41	(0.98)	23	(0.91)	25	(1.48)	48	(1.14)
Group 2: both mitral and aortic damaged	L. I.	39	(1.65)	19	(1.18)	58	(1.46)	83	(3.52)	52	(3.22)	135	(3.40)
	B. H.	27	(0.86)	20	(1.62)	47	(1.08)	61	(1.95)	44	(3.56)	105	(2.40)
	C. R.	6	(0.24)	9	(0.53)	15	(0.36)	25	(0.99)	7	(0.41)	32	(0.76)
Groups 1 and 2 combined	L. I.	69	(2.92)	73	(4.52)	142	(3.57)	103	(4.36)	117	(7.24)	220	(5.53)
	B. H.	61	(1.95)	29	(2.35)	90	(2.06)	82	(2.62)	76	(6.15)	158	(3.61)
	C. R.	19	(0.76)	37	(2.19)	56	(1.33)	48	(1.91)	32	(1.89)	80	(1.90)
Group 3: aortic damaged; mitral normal	L. I.	25	(1.06)	12	(0.74)	37	(0.96)	42	(1.78)	6	(0.37)	48	(1.20)
	B. H.	15	(0.48)	6	(0.49)	21	(0.47)	42	(1.34)	12	(0.97)	54	(1.24)
	C. R.	9	(0.36)	2	(0.12)	11	(0.26)	19	(0.75)	3	(0.18)	22	(0.52)

*L.I., Long Island series.
B.H., Bellevue Hospital series
C.R., Costa Rican series.

Bellevue groups occupy an intermediate position in all but two categories. The Costa Rican series has a slightly higher incidence than the Bellevue series of stenotic lesions of the mitral valve in males and of acute and mild lesions of the mitral valve in females. The constancy of the relative incidence of rheumatic valvular lesions in the three series is more apparent when all types are grouped together. There are about three times as many examples of rheumatic endocarditis in the Long Island series as in the Costa Rican, and about twice as many in the Bellevue series as in the Costa Rican. One noteworthy variable finding is observed when the incidence of various types of rheumatic valvular lesions in the three series is compared, namely in the Costa Rican series a relatively small proportion have rheumatic involvement of both mitral and aortic valves.

The differences in incidence of rheumatic lesions do not necessarily reflect differences in the incidence of the disease in the entire populations from which these three hospitals receive patients. Both the Bellevue and Long Island hospitals serve essentially the same type of persons and yet show marked differences in the incidence of rheumatic lesions. This indicates that the smaller incidence in the Costa Rican series is not necessarily the result of decreased susceptibility of the Costa Rican population as a whole because of environmental or racial backgrounds. The hospital San Juan de Dios receives patients from both inland mountainous areas and costal lowland areas. The incidence of rheumatic disease in these two regions may vary greatly. However, the finding that the mitral valve alone is involved in a relatively high percentage of the Costa Rican cases does suggest that rheumatic heart disease tends to run a milder course in that country. Another equally valid explanation to account for this difference may be offered. Because of the prevalence of tuberculosis, malnutrition, and helminthic and protozoal diseases, rheumatic patients in Costa Rica may die at a relatively young age before the rheumatic lesions have progressed to advanced stages. In the Costa Rican series 51.1 per cent of the males and 62.6 per cent of the females were between 10 and 50 years of age at death. The corresponding age period in the Bellevue series contained only 28.4 per cent males and 34 per cent females. In the Long Island series there were 29.4

per cent males and 32.1 per cent females in this age period. No very satisfactory explanation can be offered to account for the differences in incidence of rheumatic lesions between the Bellevue and Long Island series. It is possible, however, that the Long Island College Hospital, and even the Kings County Hospital, treat patients of a somewhat higher economic level than does Bellevue Hospital.

In the male groups in which only the aortic valve was calcified, the three series show the same order of frequency as do the groups with definite rheumatic lesions. The Long Island series has the highest percentages; the Bellevue series is second; and the Costa Rican is third. A striking preponderance of calcareous aortic stenosis in the male is noted in all three series. This is in accord with the sex incidence of this lesion as reported in most published series. Of the 1,615 females in the Long Island group only six had calcareous aortic stenosis, and of the 1,691 females in the Costa Rican series only three had this lesion. The number of females with calcareous aortic stenosis in these two series is so small that percentages obtained from it are obviously without statistical value. Therefore the finding of a higher incidence of aortic stenosis among females in the Bellevue series over that in the other two, as shown in Table I, is probably a chance variation. As noted in most published analyses on the incidence of calcareous aortic stenosis, an older age group is involved than is the case with the accepted rheumatic types of lesions. The median age for the groups of aortic stenosis is as follows: in the Long Island series, males 64 years, females 67 years; in the Bellevue series, males 67 years, females 66 years; and, in the Costa Rican series, males 47 years, females 60 years. If all the definite rheumatic lesions in which one or more valves were stenotic are grouped together, the following median ages for the three series are obtained: Long Island series, males 40 years, females 41 years; Bellevue series, males 50 years, females 47 years; Costa Rican series, males 44 years, females 37 years.

It is thus seen that certain features of both the rheumatic groups and the groups with only aortic valve involvement are constant in all three series. This may be taken as evidence that the lesions of rheumatic disease follow a fairly fixed pattern in different populations and in these two different parts of the world. It is therefore reasonable to expect that, if calcareous aortic stenosis is rheumatic in origin, its incidence should bear some fixed relation to the incidence of other rheumatic lesions.

In Table II the incidence of the various types of valvular lesions is compared in the three autopsy series. All acute, mild, and stenotic lesions of the mitral valve alone, and of both mitral and aortic valves, are grouped together for males, and for both males and females in each series. Similarly, all acute, mild, and stenotic lesions involving only the aortic valve are grouped together for males and for males and females. The ratios between the two corresponding groups of males in each series are extremely constant. There are about two and one-half times as many cases with established types of rheumatic lesions as with lesions limited to the aortic valve in each series. In other words, in series showing a high incidence of rheumatic endocarditis, the incidence of calcareous aortic stenosis is correspondingly high and vice versa.

A very small number of cases of acute verrucous endocarditis limited to the aortic valve is included in each series. These showed the characteristic inflammatory changes of rheumatic endocarditis. If calcareous aortic stenosis is rheumatic in origin, then this acute lesion probably represents an early stage of the lesion. In comparing the incidence of calcareous lesions of the aortic valve alone to definite rheumatic lesions in which the mitral valve is involved, it

TABLE II. THE RELATIVE INCIDENCE OF LESIONS OF THE AORTIC VALVE (MITRAL VALVE UNDAMAGED) AND OTHER VALVULAR LESIONS IN THREE AUTOPSY SERIES

	AORTIC LESIONS (MITRAL UNDAMAGED)				OTHER VALVULAR† LESIONS		RATIO OF OTHER VALVULAR LESIONS TO CALCAREOUS AORTIC LESIONS	RATIO OF OTHER VALV- ULAR LESIONS TO TOTAL AORTIC LESIONS
	CALCAREOUS* DEFORMITY		TOTAL†					
	NO.	%	NO.	%	NO.	%		
Males								
Long Island	60	(2.58)	67	(2.84)	172	(7.29)	2.8:1	2.6:1
Bellevue	56	(1.78)	57	(1.82)	143	(4.57)	2.6:1	2.5:1
Costa Rica	23	(0.90)	28	(1.11)	67	(2.67)	3.0:1	2.4:1
Total (Males and Females)								
Long Island	73	(1.84)	85	(2.15)	362	(9.10)	4.9:1	4.2:1
Bellevue	74	(1.69)	75	(1.71)	248	(5.68)	3.4:1	3.3:1
Costa Rica	26	(0.62)	33	(0.78)	136	(3.23)	5.2:1	4.1:1

*Includes all calcareous deforming lesions of aortic valve; acute verrucous lesions excluded.

†Includes all acute, mild, and stenotic lesions of the aortic valve.

‡Includes all acute, mild, and stenotic lesions of mitral valve alone and of both mitral and aortic valve.

becomes a moot question whether acute verrucous aortic lesions should be included or excluded. However, the number of these cases is so small that their exclusion does not significantly alter the ratio between the incidence of calcareous lesions of the aortic valve and all other definite types of rheumatic valvular disease (Table II).

As noted previously, the incidence of calcareous aortic stenosis in females is so low that the relatively small groups analyzed do not provide enough examples to give constant percentage values. In the Long Island group of eighteen females with lesions limited to the aortic valve, five showed acute verrucous endocarditis, seven had mild deformities with aortic insufficiency, and only six were stenotic. Of the five females with lesions limited to the aortic valve in the Costa Rican series, two showed acute verrucous endocarditis, and three were stenotic. Because of the small number of females with aortic stenosis in these two series their ratios are not shown in the table. When males and females are grouped together, the ratio of rheumatic endocarditis to the aortic lesions is increased because of the low incidence of aortic lesions in females. The ratios of the Long Island and Costa Rican group are still constant. The ratio of the Bellevue group is slightly lower, but this discrepancy is probably without significance. These findings suggest that the mechanisms involved in the production of aortic valve lesions alone and of recognized types of rheumatic valvular lesions are probably fundamentally the same.

It is, of course, quite possible that the close relationship between the incidence of aortic valve lesions alone, and other types of rheumatic endocarditis, is coincidental. As noted above, a high percentage of the patients in the Costa Rican series died before the age of 50 years. It was also noted that calcareous aortic stenosis occurs most frequently in advanced age groups. It is therefore possible that the low incidence of calcareous aortic stenosis in the Costa Rican series is not related to the low incidence of rheumatic disease, but rather to the short survival period. In Table III the incidence of calcareous aortic stenosis is shown in the groups of persons dying at an older age than 50 years in each of the three series. Even in these older age groups, the Long Island series has the highest incidence of aortic lesions. The Bellevue series is second, and the Costa Rican is third. In males, the ratio between the three series is approximately 3:2:1. This is about the same relative incidence of all accepted rheumatic valvular lesions in the three series (Table I). When females who died after they had reached the age of 50 years are included, the incidence of aortic lesions

in the Bellevue series approximates that in the Long Island group. As already pointed out, this is probably because the incidence of aortic stenosis in this sex is so low that accidental variation plays a role in the small number of females included in the analysis. Even here, however, the Costa Rican series has only one-half as many examples of aortic lesions as do the other two series. It is obvious therefore that the low incidence of aortic lesions in the Costa Rican series is independent of age.

TABLE III. THE INCIDENCE OF LESIONS OF THE AORTIC VALVE (MITRAL VALVE UNDAMAGED) IN GROUPS OF PATIENTS OVER 50 YEARS OF AGE IN THREE AUTOPSY SERIES

	TOTAL	NUMBER WITH LESIONS	PERCENTAGE
<i>Males</i>			
Long Island	1,378	41	3.0
Bellevue	2,168	39	1.8
Costa Rica	885	11	1.2
<i>Males and Females</i>			
Long Island	2,234	46	2.1
Bellevue	2,908	56	1.9
Costa Rica	1,254	13	1.0

SUMMARY

The incidence of rheumatic endocarditis of the mitral valve alone, and of the mitral and aortic valves together, in three independent series of autopsies is compared. Differences in the total incidence of valvular lesions were noted in each of the three series. These differences cannot be attributed to racial or geographical factors alone, since two of the series represent cases from essentially the same types of population in the New York area. However, the relative incidence of each type of valve lesion is constant in the three series. Mitral stenosis is more common in women than in men in each series. The incidence of calcareous deforming lesions, limited to the aortic valve, is also determined in the three autopsy series and is found to vary constantly with the incidence of rheumatic lesions in each of the three series. In males, lesions of the mitral valve alone, together with lesions of both mitral and aortic valves, are about two and one-half to three times as common in each series as are calcareous deforming lesions limited to the aortic valve. Lesions of the aortic valve only are more common in males and involve an older age group than do the other types of rheumatic lesions. The incidence of lesions of the aortic valve only, in the groups surviving longer than 50 years in each series, is relatively the same as for the entire age group in each series, however.

CONCLUSION

The constant ratio of the incidence of calcareous aortic stenosis to the incidence of accepted types of rheumatic endocarditis suggests that the two lesions have a common etiology.

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THE ELECTROCARDIOGRAM IN PNEUMOPERITONEUM

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CLINICAL OBSERVATIONS

THE introduction of pneumoperitoneum on a larger scale in the treatment of pulmonary tuberculosis¹ has made it possible to study the effect of a markedly raised diaphragm on the heart and circulation. Two outstanding features emerge from the observations. First, cardiovascular distress seldom occurs in such patients, even if one side of the diaphragm rises as high as the second rib anteriorly. Second, an electrocardiogram is obtained which resembles the pattern of acute cor pulmonale.² In this paper both these observations will be supplemented by further investigations of the vital capacity and of a detailed electrocardiographic analysis with an attempt to derive from the findings the geometric displacement of the heart.

Several hundred pneumoperitonea have been induced during the last three years at Clare Hall Hospital, and only one case is known in which the patient, who suffered from extensive bilateral tuberculosis with cavitation and was, in fact, in a hopeless condition, developed edema, cyanosis, and breathlessness. Whether this clinical picture can be ascribed to the mere displacement of the heart following the elevation of the diaphragm or to a failing myocardium as a sequela of tuberculous toxemia remains undecided. Attacks of transient breath-

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lessness do occur following the induction of pneumoperitoneum or after the first three or four refills, but these have been of moderate degree, never causing distress, and have disappeared as the refills went on in the ensuing weeks. They often appear more conspicuously when abdominal adhesions are present and when the initial slight abdominal discomfort prevents the patient from breathing as freely as he usually does later on. It seems at this juncture advisable to emphasize that the technique employed in this hospital aims at the *gradual* rise of the diaphragm previously paralyzed by phrenic crush. A sudden marked elevation of the diaphragm is liable to cause distress. The technique, first applied extensively in England by Clifford-Jones and Macdonald,¹ follows.

TECHNIQUE

The patients dealt with in this paper had a phrenic crush performed on one side three to four weeks before the induction of the pneumoperitoneum. No premedication was given before the induction. The patient lay comfortably in the recumbent position. The skin was injected with a local anesthetic about 1 inch below the left costal margin. A dry medium-sized or long-sized Morland A-P refill needle, which was connected with the open manometer of an A-P box, was pushed slowly through the abdominal wall and the peritoneum. The passing of the needle through the peritoneum was usually marked by a click, and the manometer might show a sudden movement. Usually no pressure was recorded until air had been introduced. Air was run in slowly, and the pressure was checked. Under frequent control of pressure, 600 to 1,000 c.c. were then

TABLE I

DATE	TREATMENT	VITAL CAPACITY IN C.C. OF AIR, BEFORE REFILL	REFILL IN C.C. OF AIR	VITAL CAPACITY IN C.C. OF AIR, AFTER REFILL
6/4/44	Phrenic crush (R)			
11/3/44		2,500		
15/3/44	Induction of P.P.			
21/3/44		2,500	1,400 (+3+5)*	2,700
29/3/44		3,000	1,000 (+5+10)	2,900
5/4/44		2,900	1,200 (+7+14)	2,700
12/4/44		3,000	900 (+11+8)	2,700
19/4/44		3,000	1,000 (+17+11)	2,800
26/4/44		3,000	1,000 (+16+10)	2,100

This table shows some rise of the vital capacity figures after a period of six weeks' treatment.

*The figures in parentheses indicate the initial and the final intra-abdominal pressures in centimeters of water.

TABLE II

DATE	TREATMENT	VITAL CAPACITY IN C.C. OF AIR BEFORE REFILL	REFILL IN C.C. OF AIR	VITAL CAPACITY IN C.C. OF AIR AFTER REFILL
13/1/44	Phrenic crush (L)			
10/2/44		3,200		
10/2/44	Induction of P.P.			
15/2/44		3,000	1,100 (+8+11)*	3,000
22/2/44		3,100	1,000 (+9+12)	3,500
7/3/44		3,300	1,500 (+10+10)	3,100
14/3/44		3,100	1,400 (+9+11)	2,700
21/3/44		3,100	1,400 (+7+15)	3,000
29/3/44		-	1,000 (+15+16)	-
5/4/44		-	1,200 (+14+12)	3,200
12/4/44		3,400	800 (+10+12)	3,100
19/4/44		3,200	800 (+8+9)	3,000
26/4/44		3,200	1,000 (+8+10)	3,100

This table shows no change of the vital capacity after a period of more than two months' treatment. The left diaphragm was markedly raised.

*The figures in parentheses indicate the initial and the final intra-abdominal pressures in centimeters of water.

introduced. No definite ruling as to the final pressure can be given; +8 or +10 cm. of water was a common finding, but it sometimes rose as high as +25 cm. when adhesions were present. To ascertain the rise of the diaphragm the patient was fluoroscoped immediately after the induction. The first refill of about 800 c.c. was given a day or two after the induction, and one more refill was given on the third or fourth day, according to the elevation of the diaphragm. As soon as an adequate rise was established, weekly refills of 800 to 1,200 c.c. were given.

VITAL CAPACITY

In order to find an answer to the surprising lack of dyspnea, the vital capacity was measured in a number of cases, some of which are shown in Tables I, II, III, IV, and V. In addition, a larger number of cases have been summarized in a curve (Fig. 1). All points in this graph were obtained by dividing the estimated vital capacity by the initial vital capacity figure in each instance, thus making all the data for the different patients comparable with one another.

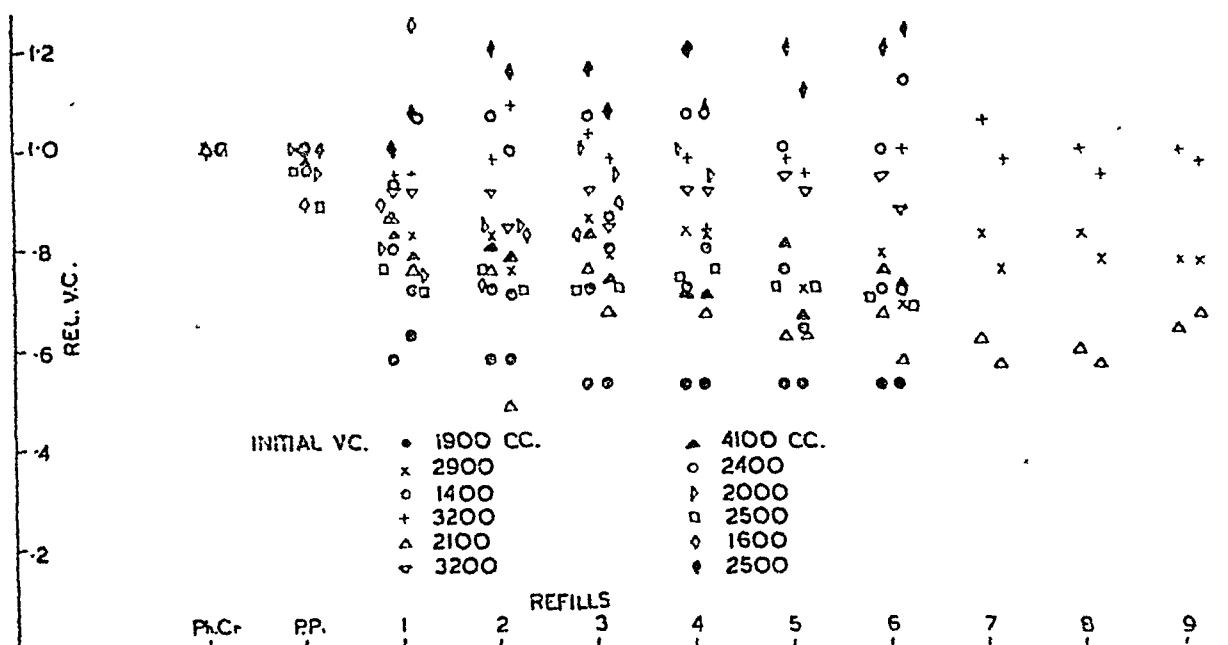


Fig. 1.—Relative vital capacities of twelve cases at various stages of the treatment. The relative vital capacity is the measured capacity divided by the initial capacity. *Ph.Cr.* indicates phrenic crush; *P.P.*, indicates induction of pneumoperitoneum.

The conclusion we have drawn from these data is that they do not show a uniform trend. In several cases, after a series of refills, no marked decrease of the vital capacity was noted; some even showed a slight increase and, in very few of the cases showing a drop, was the vital capacity grossly affected.

TABLE III

DATE	TREATMENT	VITAL CAPACITY IN C.C. OF AIR BEFORE REFILL	REFILL IN C.C. OF AIR	VITAL CAPACITY IN C.C. OF AIR AFTER REFILL
18/2/44	Phrenic crush (R)			
15/3/44	Induction of P.P.	3,200	1,000 (+1+5)*	
21/3/44		2,900	1,200 (+5+11)	2,900
29/3/44		2,900	1,000 (+7+14)	2,700
5/4/44		2,900	1,000 (+8+12)	2,700
12/4/44		2,900	1,000 (+9+13)	2,900
19/4/44		3,000	1,000 (+7+9)	2,900
26/4/44		3,000	900 (+7+8)	2,800

This table shows hardly any change of the vital capacity during the period of six weeks. A single refill of 1,000 c.c. affected the vital capacity only slightly.

*The figures in parentheses indicate the initial and the final intra-abdominal pressures in centimeters of water.

TABLE IV

DATE	TREATMENT	VITAL CAPACITY IN C.C. OF AIR BEFORE REFILL	REFILL IN C.C. OF AIR	VITAL CAPACITY IN C.C. OF AIR AFTER REFILL
29/2/44	Phrenic crush (L)			
11/3/44		4,100		
21/3/44	Induction of P.P.	3,500	1,200 (+6+8)*	3,300
29/3/44		3,400	1,000 (+5+7)	3,300
5/4/44		3,500	1,200 (+4+10)	3,100
12/4/44		3,500	900 (+4+7)	3,000
19/4/44		3,400	900 (+4+7)	2,800
26/1/11		3,200	900 (+5+7)	3,100

This table shows an initial decrease of the vital capacity of 600 cubic centimeters. After this there was no further marked change. The vital capacity remained high.
*The figures in parentheses indicate the initial and the final intra-abdominal pressures in centimeters of water.

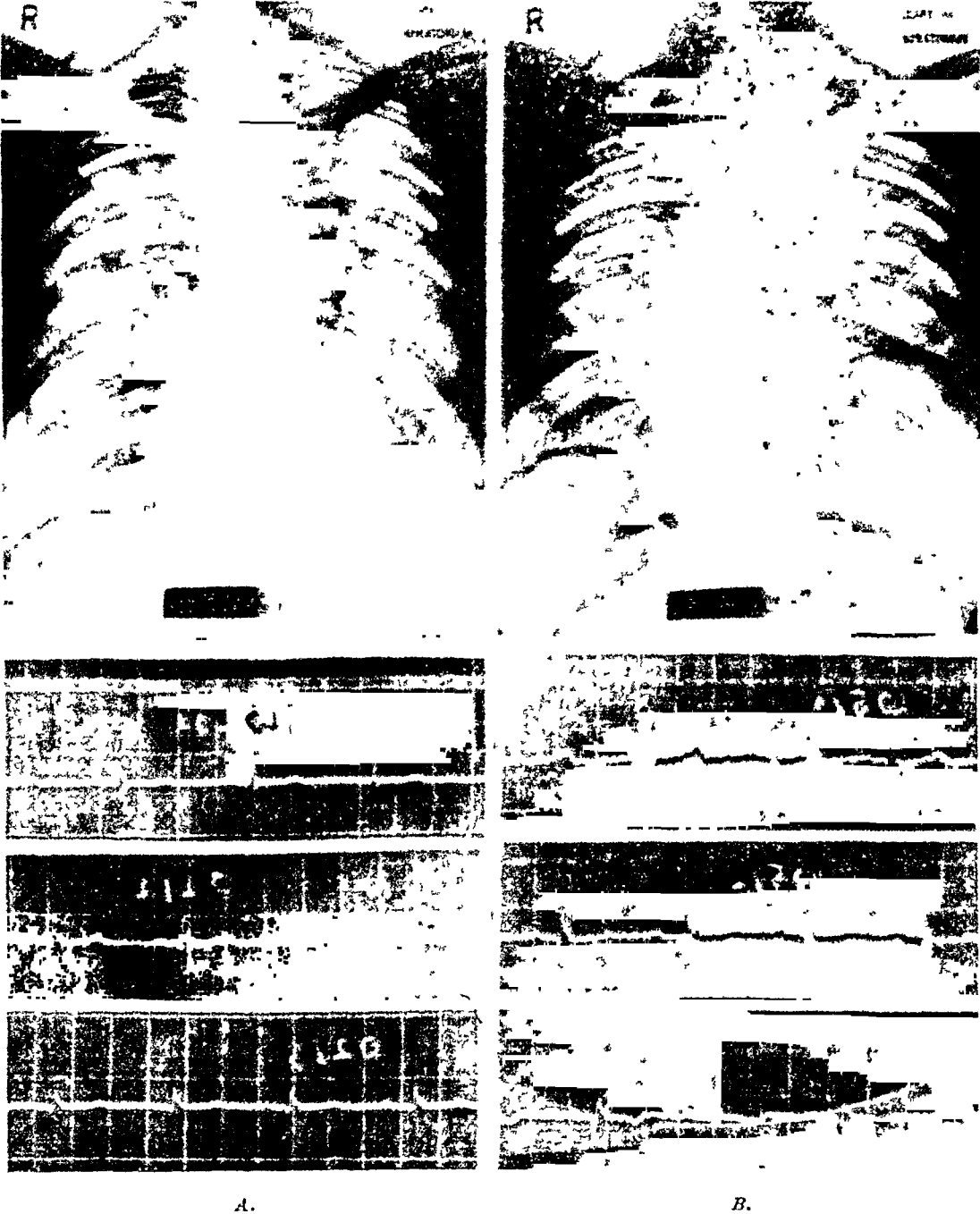


Fig. 2.—H. W.: A, Slight left diaphragmatic rise after left phrenic crush. B, During pneumoperitoneum treatment. Marked rise of the left paralyzed diaphragm. Some rise of the right diaphragm. The electrocardiogram shows some flattening of S-T, a conspicuous Q₁ and T₁ inverted.

TABLE V

DATE	TREATMENT	VITAL CAPACITY IN C.C. OF AIR BEFORE REFILL	REFILL IN C.C. OF AIR	VITAL CAPACITY IN C.C. OF AIR AFTER REFILL
18/2/44	Phrenic crush (L)			2,200
14/3/44	Induction of P.P.	2,400	1,000 (+1+6)*	1,800
20/3/33		1,900	1,400 (+8+11)	1,800
27/3/44		1,900	1,400 (+7+10)	1,800
3/4/44		1,800	1,000 (+6+9)	1,800
11/4/44		1,850	800 (+7)	1,900
17/4/44		1,800	900 (+6+9)	1,800
24/4/44		1,750	800 (+5+7)	1,700

This table shows an appreciable decrease of the vital capacity in a period of six weeks' treatment.

*The figures in parentheses indicate the initial and the final intra-abdominal pressures in centimeters of water.

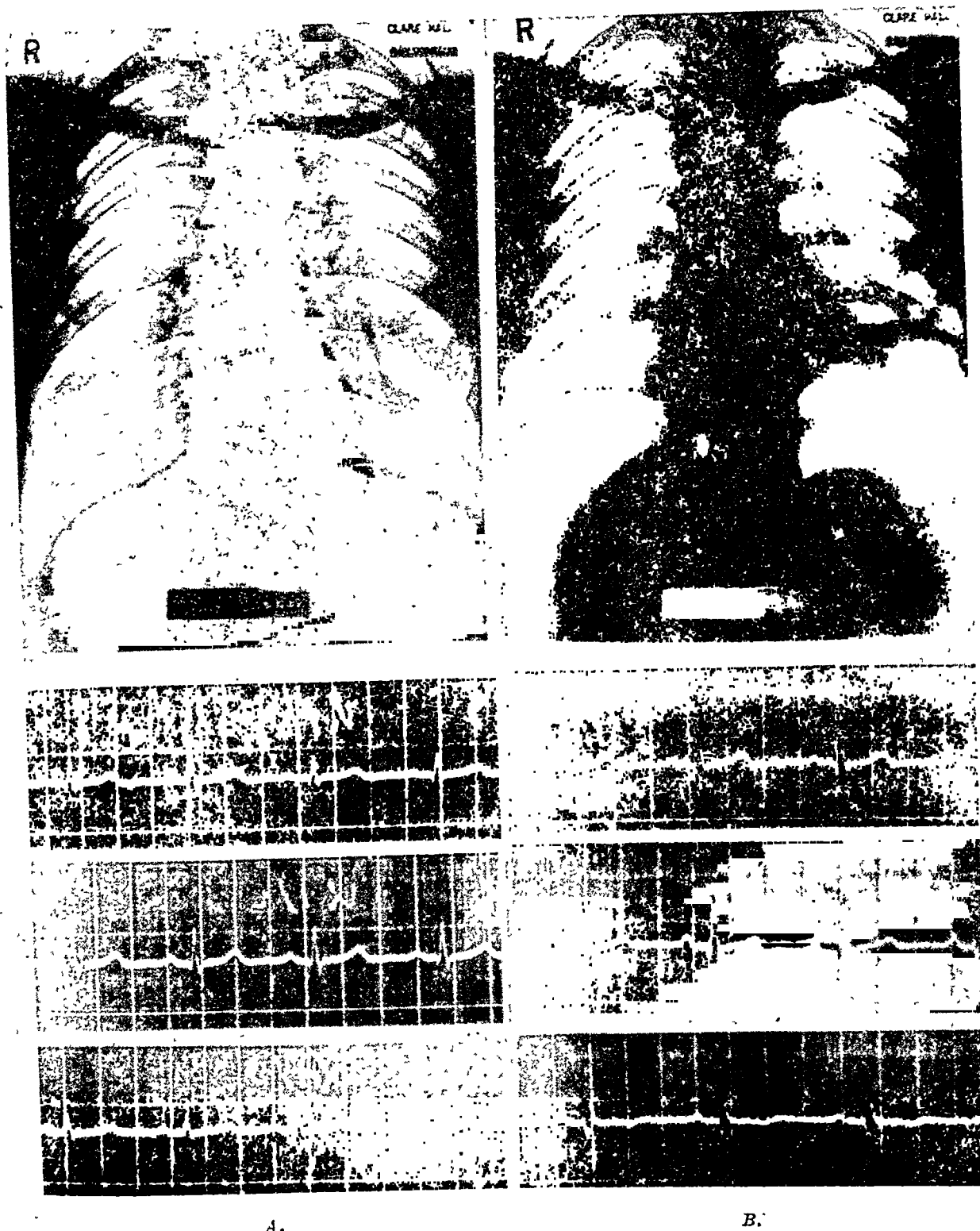


Fig. 3.—K. T.: A, Before left phrenic crush. B, During treatment with pneumoperitoneum. Both sides of the diaphragm raised; the left more than the right. Electrocardiogram: S-T becomes slightly flatter; Q₂ is conspicuous, and T₂ is inverted.

ELECTROCARDIOGRAPHIC PATTERN

The electrocardiographic pattern is characterized by the following features: Soon after the rise of the diaphragm, whether it be the right side, the left side, or both, the S-T segment in Lead II flattens. In Lead III a conspicuous Q wave followed by a small R and an inverted T deflection occurs. This is an almost constant picture, the only variations being that these characteristics may be more or less pronounced. Typical examples are shown in Figs. 2, 4, and 5. Figs. 2 and 3 illustrate the condition before the induction and after a number of refills. In Fig. 4 the first electrocardiogram (A) was taken at the height of the diaphragmatic rise and exhibits all the features described. Then the pneumoperitoneum was abandoned, and the second tracing (B) was taken after the diaphragm had descended. The pattern has become normal again. Fig. 5 is of a patient who showed a typical pneumoperitoneum pattern as the diaphragm

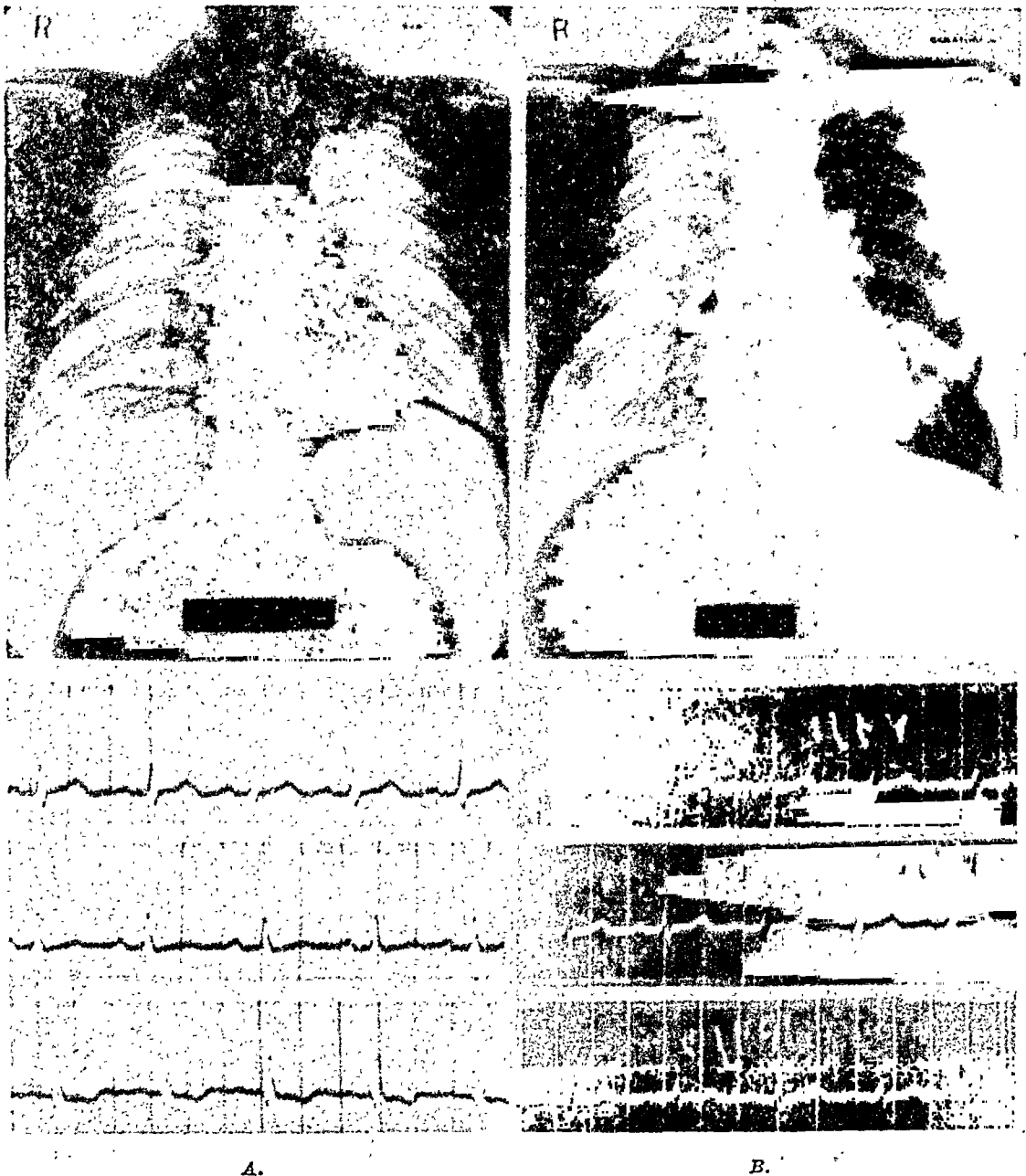


Fig. 4.—A. P.: A, X-ray and electrocardiogram at the height of the diaphragmatic rise. S-T₂ is flattened, Q₃ is present, and T₃ is inverted. B, Pneumoperitoneum abandoned. The diaphragm has descended to its lowest level. The electrocardiogram now shows a normal S-T₂ and S-T₃. No Q₃ is present.

rose; then the refills were discontinued, the diaphragm came down, and with it the electrocardiogram approached the normal, though not completely, as the phrenic paralysis persisted and the diaphragm did not descend to its lowest level.

The electrocardiograms as demonstrated here represent only the initial and final patterns. The characteristic picture usually occurs soon after the early refills.

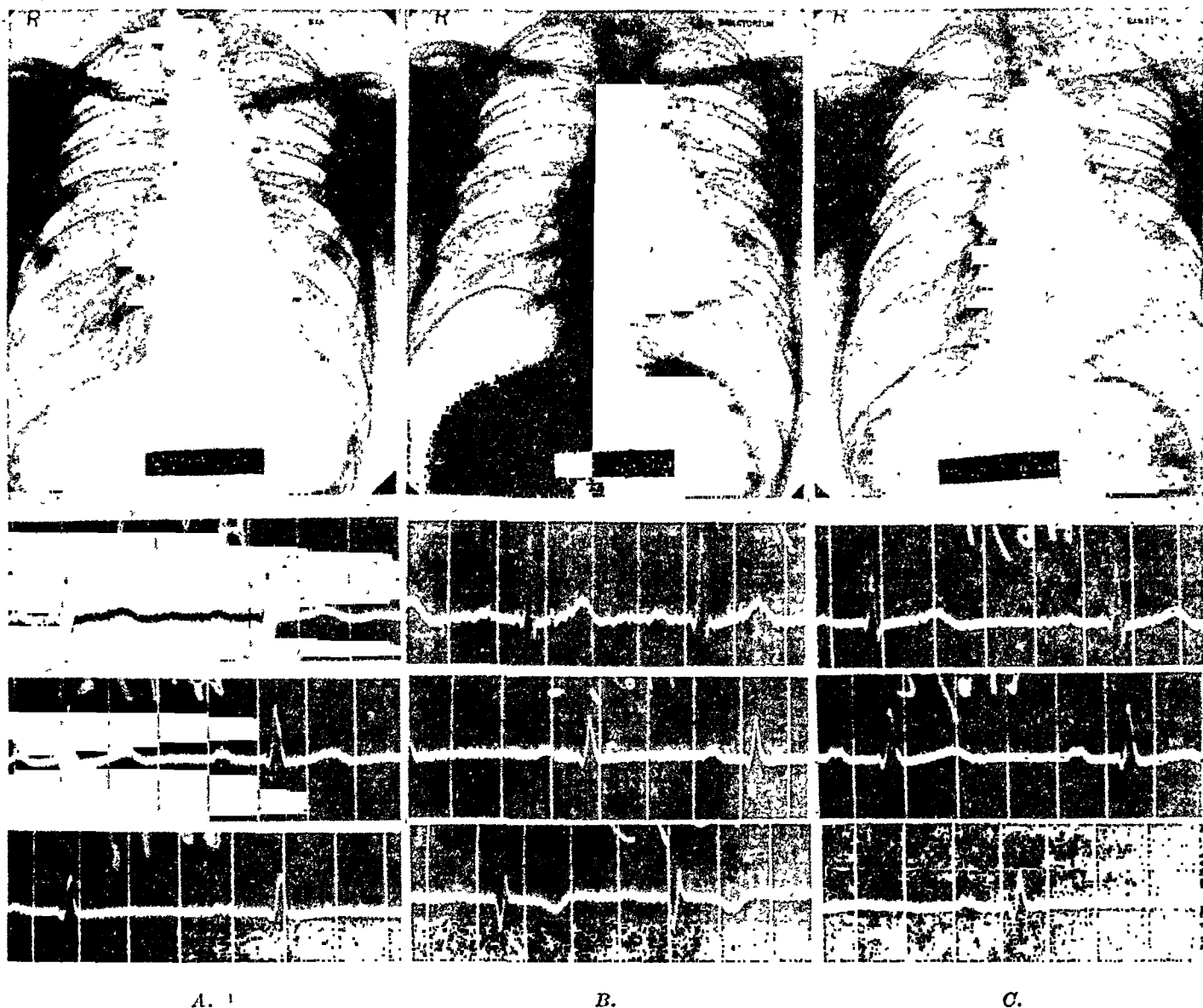


Fig. 5.—J. H.: A, Left diaphragm is slightly raised after left phrenic crush. B, During treatment with pneumoperitoneum both sides of diaphragm raised; left higher than the right. The electrocardiogram shows flattening of S-T₂, marked Q₂, and inverted T₂. C, Pneumoperitoneum abandoned; diaphragm approaching previous level. Electrocardiogram: T₂ reappears, Q₂ becomes smaller, and R₂ taller. The inversion of T₂ has disappeared.

DISCUSSION

The electrocardiograms characteristic of pneumoperitoneum resemble to a certain extent the Q₃-T₃ pattern of coronary thrombosis involving the posterior wall, although with pneumoperitoneum we do not find that the S-T segment in Lead III ever becomes really dome-shaped. No clinical symptoms, however, suggesting coronary thrombosis have been noted. Moreover, no clinical signs such as anterior thoracic pain, fainting attacks, or sudden onset of dyspnea have been recorded. Therefore, the suggestion that these electrocardiograms represent the pattern of acute cor pulmonale due to pulmonary embolism, can be dismissed. However, it is conceivable that a reduction of the bed of the pul-

monary circulation is brought about by the elevation of the diaphragm, thus straining the right heart. This seems unlikely for the following reasons. First, the vital capacity—an important though not the sole measure of pulmonary function—does not show any gross diminution; sometimes even a slight rise occurs. Second, in collapse therapy, such as artificial pneumothorax after adhesion section, or after a nine-rib thoracoplasty, much larger areas than those affected by pneumoperitoneum are usually collapsed without the electrocardiogram, even approaching the pneumoperitoneum pattern as described previously. Right axis deviation with a deep S deflection in Lead I is often one of the findings when the heart is displaced by these collapse measures. Third, the pattern obtained with a raised diaphragm is reversible, and can be brought back to normal with the descent of the diaphragm.

It thus appears that we have exhausted all the known clinical possibilities of accounting for the electrocardiographic changes observed. The only explanation left is to assume that the heart remains functionally intact and that the changes in the electrocardiogram are brought about merely by a geometric displacement of the heart. The tracings were therefore analyzed from this point of view.

METHOD OF ANALYSIS

For the purpose of the present analysis it is assumed that an electrical axis determination is equivalent to a determination of the geometric position of the heart. Thus, the electrical axes are used as pointers fixed to the heart, following and indicating its displacements. Some of the changes could be studied from the alteration of the heart's position in the roentgenogram, but the measurements are not reliable. The electrical methods, however, were found to convey a more detailed picture of its movements in three dimensions.

Two major difficulties had to be overcome before electrical axis determinations could be carried out. One of these, the fact that the instrument available could only record a single lead at a time, was purely technical. All published methods of electrical axis determination are based on the simultaneous recording of at least two of the standard leads; from these two tracings the position of the electrical axis in the frontal plane at any chosen instant can be worked out by one of several well-established methods. The second difficulty is more fundamental. As we wish to correlate the displacement of the electrical vector with that of the heart itself, it is necessary to carry out the axis determination at a well-defined point of the heart cycle. However, the very change in the electrocardiographic pattern we are interested in makes it impossible to recognize with any certainty the phases of the cycle before and after the displacement of the heart. This second difficulty would persist even if it were possible to record two leads simultaneously.

The application of a concept introduced by Wilson, MacLeod, Barker, and Johnston,³ and used very extensively since by Ashman, Byer, and Bayley⁴ offered a way out of both these difficulties. These authors have defined as the "ventricular gradient" and the "QRS vector" a pair of electrical axes which represent the total average activity of the whole ventricular complex and of the QRS complex respectively. The averaging process here refers both to the direction and the intensity of the individual vectors making up the electrical activity of the heart. As a result of the calculation we obtain new vectors of which we know both the direction and the magnitude (length), the latter being designated as manifest value. Being averages over the whole or a well-defined

part of the QRS-T complex, these vectors are not tied to any particular phase and can therefore be used as indicators to denote any changes in the position of the heart. Ashman and Byer⁴ may have had an application such as this in mind when they correlated the direction of the average vectors with the position of normal human hearts, although the method has apparently not been applied to cases where the position was actually changed in the same patient.

Details of the method used are not of great interest. Suffice it to say that the electrocardiograms were projected on graph paper and the outlines were drawn. The areas under the enlarged electrocardiograms so obtained were determined by counting those squares above the zero line as positive, and those below as negative. The sum of the squares counted for any one of the leads (averaging in each case over three cycles) represents the component of the average vector in the direction given by the points at which the lead was taken.

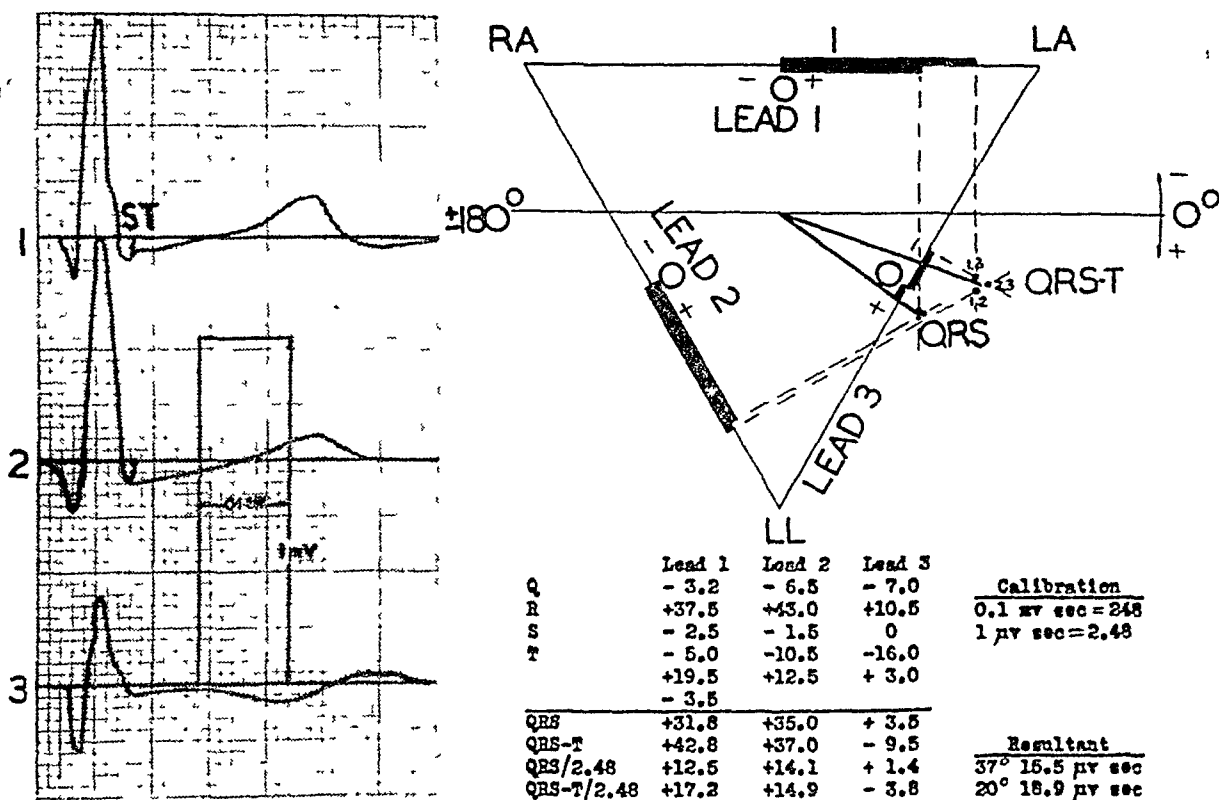


Fig. 6.—Illustrating method of evaluation. The areas under the different parts of the electrocardiographic tracings are tabulated and added to give those of QRS and QRS-T. The latter divided by the area occupied by 1 μ v second gives the components of the average vectors along the sides of the Einthoven triangle. These components are marked by heavy lines inside the triangle for QRS and outside the triangle for QRS-T. The resultant vectors are constructed from their components as shown; their lengths and directions are read off the diagram. Where the three values of the resultant vector (marked 1/2, 2/3, 1/3) differ, the center of the little triangle formed is the average of the three values given in the table. The figure also illustrates the choice of the demarcation between S and T.

An example of the procedure is given in Fig. 6. The areas measured were standardized by the deflection produced by impressing the usual calibration voltage of 1 millivolt on the recording galvanometer; knowledge of the standardized deflection and of the time scale recorded in each case enables one to express these areas in terms of millivolt-seconds (mv) or microvolt-seconds (μ v). The directions of the vectors were determined by using the chart of Carter, Richter, and Greene.⁵ Measurements of the values in any of the two leads allow the determination of the direction and the manifest value of an electric heart axis as projected on to the frontal plane; here all three leads were utilized in order to check the validity of the Einthoven triangle. In this way three values were obtained in each case, the averages of which are quoted in Table VI. All the values are tabulated for all measurements from one of the patients, in order to

convey an idea of the accuracy obtainable. It is considered that the agreement of the values justifies the method adopted for evaluating the electrocardiograms; but it should be pointed out that the accuracy is lower for patients with lower voltages in their electrocardiograms.

INTERPRETATION AND RESULTS

When one attempts to determine the QRS vector a difficulty of interpretation arises which is probably less pronounced with a normal human heart than with the displaced heart under consideration. The displacement of the heart manifests itself by a strong deviation of the S-T segment from the zero line, in particular in Lead III. This means that if the definition given by Ashman and Byer⁴ ("the area of S is the area below the upper edge of the S-T junction, or, if that junction is deviated, below the level of the base line . . .") is followed literally, misleading results will be obtained; the QRS complex would seem to last very much longer in one of the leads than in the other two. Since there is no systematic method of deciding where the QRS complex finishes and the T wave begins it was often necessary to make an arbitrary decision. Fig. 6 illustrates a possible choice; the S deflection is regarded as terminating at the point where the clockwise curvature of the deflection toward the horizontal is strongest. A

TABLE VI

STAGE IN TREAT- MENT		LEADS	QRS		QRS-T		X-RAY
			ANGLE (°)	MAN. VAL. (μV SEC.)	ANGLE (°)	MAN. VAL. (μV SEC.)	ANGLE (°)
J. H.	B.	1/2	58	15.2	45	19.6	52
		2/3	68	15.2	52	19.3	
		3/1	62.5	17.4	49	21.8	
		av.	62	15.8	48	20.1	
	P. P.	1/2	29	13.4	+ 9.5	22.8	39
		2/3	26	14.5	+ 2	22.8	
		3/1	25.5	13.0	- 4	26.7	
		av.	27	13.4	+ 2	24.0	
	Ref.	1/2	0	9.6	-17	15.2	38
		2/3	+14	7.1	-14	10.6	
		3/1	+19.5	10.3	- 4.5	13.9	
		av.	+10	8.9	-11	13.0	
	P.a.	1/2	43.5	13.9	39	20.4	44
		2/3	57	13.3	47	19.4	
		3/1	51.5	16.1	45	21.8	
		av.	51	14.5	43	20.5	
A. P.	Ref.	71	6.3	12	17.2	45	
	Ref.	64	10.7	6	15.2	--	
	P.a.	73	7.4	55	18.3	43	
	P.a.	91	4.7	64	20.5	58	
	P.a.	90	5.2	45	22.4	--	
	P.a.	80	3.5	62	15.3	52	
E. A.	B.	71	5.9	28	8.5	65	
	Ref.	39	10.1	-17	11.9	--	
	Ref.	30	9.0	-21	8.5	62	
	Ref.	53	7.0	11	6.0	53	
H. W.	B.	74	7.0	65	15.3	55	
	Ph. Cr.	71	6.3	69	10.1	--	
	Ref.	62	18.0	46	18.0	--	
	Ref.	35	8.5	+ 1	14.9	--	
	Ref.	22	9.8	-12	14.5	48	
K. T.	B.	57	6.2	52	17.7	60	
	B.	63	4.7	53	13.7	--	
	Ph. Cr.	55	3.8	52	11.7	--	
	Ref.	35	15.2	22	19.6	42	

Angles of the average vectors with the horizontal and manifest values (*man. val.*) in μv seconds* at various stages of the treatment, viz.: B, before treatment; Ph. Cr., phrenic crush; P.P., induction of pneumoperitoneum; Ref., refill; P.a., pneumoperitoneum abandoned.

*Due to a fault in the instrument all the recorded voltages were low. Comparison with Ashman and Byer indicates that our voltages should be about twice those recorded. This does not affect the conclusions which are based on the relative values in the different leads.

vertical line between that point and the base line separates the S deflection from the T wave for our purposes. This arbitrary choice does not, of course, influence the values and directions of the gradient vector. That the choice was justified is demonstrated by the fulfilment of the Einthoven triangle condition for the QRS vector as shown in Table VI.

Table VI gives the manifest values and directions of the two vectors at the various stages of the pneumoperitoneum treatment. These stages are indicated by the following abbreviations: *B.* before treatment; *Ph. Cr.*, phrenic crush; *P.P.*, the induction of the pneumoperitoneum; *Ref.*, a refill; and *P.a.*, that the treatment has been abandoned, although it does not necessarily mean that the diaphragm has returned to its initial position, as phrenic paralysis may persist. The geometric position of the heart, as obtained from anteroposterior roentgenograms, is given in the last column. The procedure followed in the measurements was that described by Roesler,⁶ though it is to be borne in mind that the determination of the movement of the longitudinal axis on a roentgen film is met with great difficulties, since after the diaphragmatic rise the heart shadow can attain an entirely different shape, and sometimes the position of the apex cannot be assessed with certainty. However, a

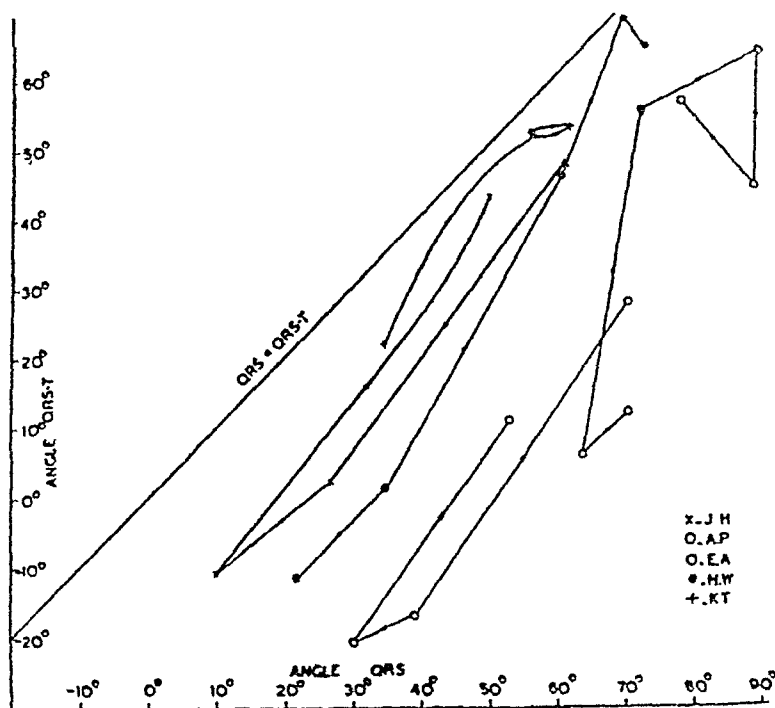


Fig. 7.—The QRS-T angles plotted against those for QRS, from Table VI. Lines with arrow heads indicate the points belonging to the same case. The points follow a well-defined trend; as the diaphragm rises the separation between QRS and QRS-T increases.

rough idea can be obtained, and from the figures shown in Table VI it is evident that the electrical vectors carry out much greater movements than are shown by the radiographic measurements. The marked rotation towards the left, as indicated by the electrical vectors, must be described as a pronounced left axis deviation. For example in the case of J. H., the QRS vector is deviated toward the left by 52 degrees and the gradient vector, by 59 degrees. In most instances the angular separation of the two vectors increases as the diaphragm rises. The angular positions of the vectors with regard to the horizontal axis in the course of P.P. are demonstrated in Fig. 7, in which, following the example of Ashman and Byer,⁴ the angle of the QRS-T complex is plotted against that of QRS complex for the cases in Table VI. It is clear that the position of the heart changes in a very well-defined manner.

Adopting the findings of Ashman, Gardberg, and Byer⁷ it is possible to describe the change of position of the heart in simple terms. These authors have shown that in the normal heart the gradient vector lies behind the longitudinal axis of the heart; the axis points slightly forward and to the left. The QRS vector lies back still further. The two vectors and the longitudinal axis of the heart lie nearly in one plane; the angle between the axis and the gradient

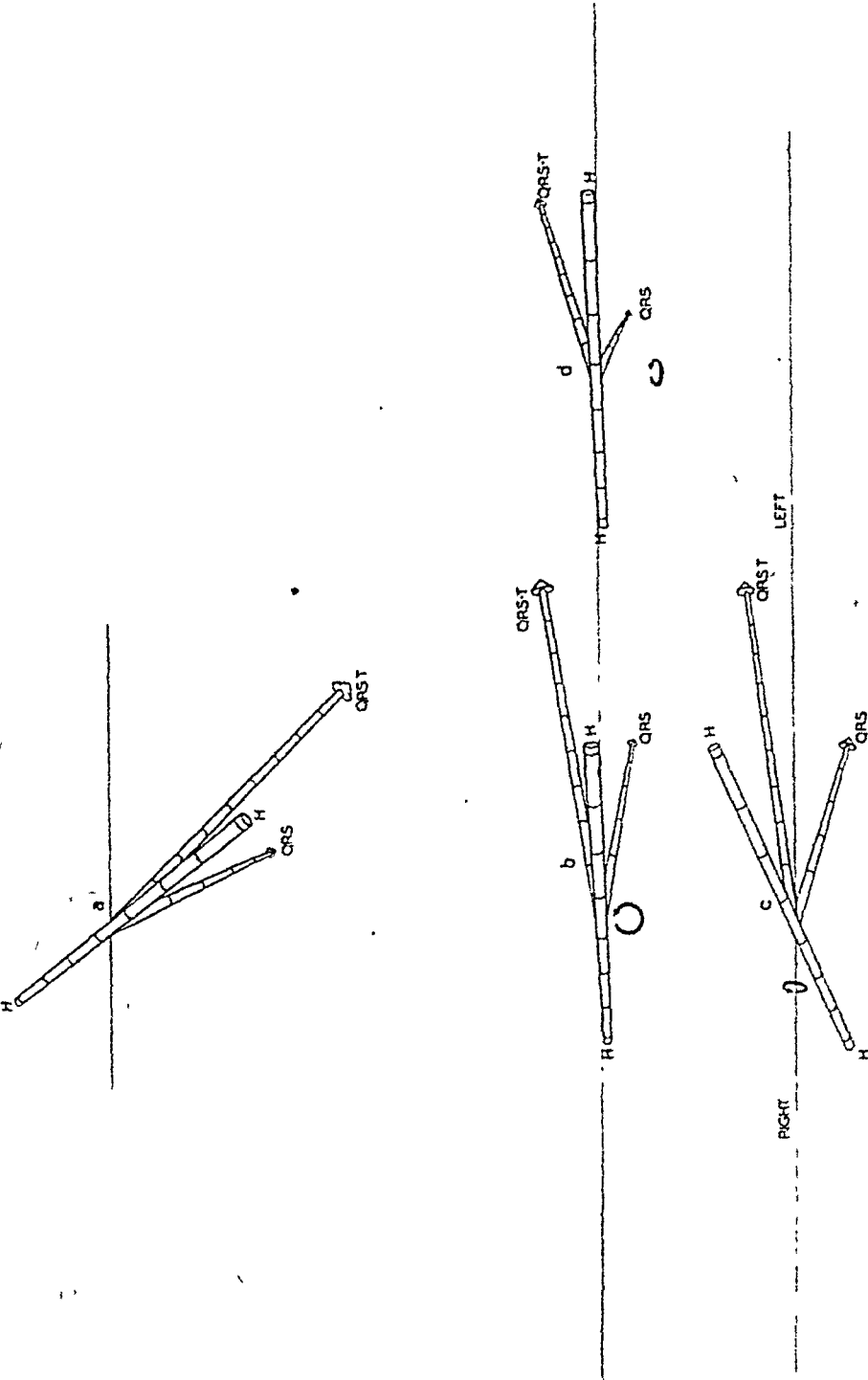


Fig. 8.—a shows the positions of the longitudinal heart axis H-H and the QRS and QRS-T vectors of a normal heart as projected onto the frontal plane. H-H points forward and to the left, QRS-T lies backward, and QRS lies back still further, all three being nearly in one plane. Rotation around an anteroposterior axis (b) merely rotates the whole configuration. Additional rotation around a horizontal axis lying in the frontal plane swings the apex of the heart upward (c), slightly increases the angle formed by QRS and QRS-T, but does not affect their length to any extent. Rotation of the heart in position (b) around a vertical axis unto (d) shortens both vectors and increases the angle between them as projected onto the frontal plane.

is approximately 60 degrees, and that between the axis and the QRS vector is approximately 90 degrees. The length of the gradient vector in space (as against its projection onto the frontal plane) is about twice that of the QRS vector. This situation is depicted for a heart in a fairly normal position in Fig. 8, a, where the length of each vector corresponds to the projection onto the frontal plane given in Table VI (J. H.). The rise of the diaphragm transfers

the vectors into positions indicated in Fig. 8, *b*, *c*, and *d*. What this movement means in terms of movement of the heart itself is best demonstrated by means of a solid model of the heart and its attached vectors, a shadow image of which is thrown onto a piece of paper representing the frontal plane. In this way it is seen that the movement of the vectors and thus of the heart consists in the main of a rotation about an anteroposterior axis. This rotation is anticlockwise if we look at the front of the body and transfers the longitudinal axis of the heart *H-II* and the vectors into the position *b*. We have seen, however, that the angle between the QRS and the QRS-T vectors increases on raising the diaphragm. This increase may be brought about in two ways: either by a rotation about a transverse axis which would leave the lengths of the vectors as measured in the frontal plane essentially unaffected (this is indicated in Fig. 8, *c*) or by a rotation around a vertical axis affecting very strongly the lengths of the projected vectors (Fig. 8, *d*). Most of the cases analyzed show rotation about the transverse axis, but the case of J. H. appears to represent a rotation about a vertical axis.

The number of cases analyzed does not allow any more general conclusions regarding the movement of the heart produced by pneumoperitoneum. It is clear that the present analysis has not exhausted the possibilities offered by this and similar operations to the study of the heart activity and in particular of the fundamental average vectors. At present the results of previous work had to be used in order to derive the movement of the heart from the electrocardiogram; the correctness of our interpretation depends entirely on these results which were derived and generalized from a study of a large number of normal human hearts in different positions of the body. The possibility of displacing the same heart, largely at will, offers the attractive prospect of determining directly the geometric relationship of the various vectors and the heart and the body.

SUMMARY AND CONCLUSION

1. The treatment of pulmonary tuberculosis with pneumoperitoneum offers the opportunity of studying the cardiovascular changes in the presence of a markedly raised diaphragm.

2. No cardiovascular distress has been observed with this kind of treatment, even if one diaphragm rises as high as the second rib anteriorly.

3. The vital capacity was measured in a number of patients; after months of treatment with pneumoperitoneum refills of 1,000 to 1,400 c.c. of air, some of them showed no change at all, others showed a slight increase, and some showed a decrease.

4. The normal electrocardiogram develops the Q_3T_3 pattern and the S-T deflection in Lead II becomes flattened. No signs of coronary thrombosis or pulmonary embolism have been noted. The pattern is reversible and becomes normal again with the descent of the diaphragm.

5. A study of the QRS vector and of the ventricular gradient demonstrates that the change of the electrocardiographic pattern is due in the main to a rotation of the heart around an essentially horizontal axis lying in the sagittal plane, the rotation to be described as anticlockwise, as one looks from front to back, i.e., the apex moves upward toward the left.

6. This accounts for the often striking distortion of the heart silhouette in the roentgenogram. The apex sometimes becomes buried in the heart shadow. Measurements of the displacement of the heart on the roentgenogram are therefore not reliable.

7. The conclusion to be drawn from the clinical observations together with the results of investigations of vital capacity and electrocardiogram is that pneumoperitoneum treatment in a tuberculous patient with a normal heart does not entail any danger from the cardiovascular point of view.

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THE RELATION OF AGE AND OTHER FACTORS TO CARDIAC SUBENDOTHELIAL HEMORRHAGE IN DOGS

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THE observation that large and small hemorrhages into the heart valves of dogs occurred with surprising frequency in examinations of animals employed for physiologic investigation prompted this study. The occurrence of cardiac subendothelial hemorrhage, spontaneously or as a result of experimental procedures, is of interest for several reasons: first because the lesions in the blood vessels responsible for such hemorrhages may be a measure of similar lesions elsewhere, which may be more difficult to observe; second, because the occurrence of such lesions may have a bearing on the age incidence of vascular disease; and third, because conditions which cause subendothelial valve hemorrhages may play a role in the etiology of such diseases as rheumatic and bacterial endocarditis. The observations reported here may provide a basis for an experimental approach to practical problems in these fields.

MATERIALS AND METHODS

Mongrel dogs of various ages were employed in this study. One hundred seventy-eight animals were used. The observations fall into three groups:

1. Observations were carried out on the hearts of eighty-six dogs of various ages, mostly killed in the laboratory for other experiments. Nineteen animals,

anesthetized with ether, were bleeders for heart-lung preparations. Nineteen were used for cerebral cortex stimulation; these, also, were anesthetized with ether. Eleven animals were killed by intravenous infusion of lanatoside C without anesthesia. Ten were anesthetized with ether and employed in respiration studies. Nine were anesthetized with nembutal for two hours and employed in intestinal absorption experiments. Eight were killed with overdoses of nembutal or ether. Eight were killed by intravenous injection of potassium cyanide solution without anesthesia. In no instance was a pressor drug employed. There were no apparent differences in the observations in the several groups, and they will be treated as one. In these animals a careful autopsy examination of the interior of the heart was made and tissues were removed for microscopic examination after fixation in Zenker-formalin solution and hematoxylin and eosin staining.

2. Forty-four dogs were studied specifically with respect to the incidence of valve hemorrhages in relation to the effects of epinephrine and pitressin.

3. Forty-eight dogs were studied specifically with relation to a possible antagonism between papaverine, vitamins P or C and epinephrine or pitressin in connection with the hemorrhagic tendency.

All animals in Groups 2 and 3 were killed by intravenous injection of 10 per cent potassium cyanide solution without anesthetization.

The presumed ages of the animals were ordinarily obtained from the dealer, who was requested to obtain as accurate information as possible from the original owners. The dogs were bought from farmers by this dealer. In a number of instances, where no such information could be obtained, the age was estimated from the condition of the teeth by an experienced animal caretaker and recorded before any other observations were made. In these estimates of age, emphasis can be placed only on the results with young and old animals.

In Series 2 and 3 the animals were treated with various agents, as indicated in each case. The sex was noted in each case, but they are not separated in the results because there was no striking sex difference in the findings.

RESULTS

1. *The Factor of Age.*—The occurrence of subendothelial hemorrhages, particularly into the mitral valve leaflets, but less often into the aortic and tricuspid valve leaflets was noted. Fig. 1 shows a typical example of a mitral valve with a punctate and larger hemorrhagic areas. Fig. 2 shows a low-power microscopic section of such a hemorrhagic valve. Fig. 3 is a high-power view of a portion of the same valve showing massive subendothelial hemorrhage. Table I shows the incidence of subendothelial hemorrhages in the valves of the hearts of dogs in relation to age. It will be seen that three and one-half times as many old dogs showed cardiac valve hemorrhage in this series of observations as did young mature animals. It is believed that no factor other than age entered into this difference because no known selective factor entered into the choice of animals for study.

2. *Hemorrhage Induced by Vasospastic Agents.*—Since the younger animals showed fewer spontaneous valve hemorrhages, the influence of various agents up-

TABLE I. SUBENDOTHELIAL HEART VALVE HEMORRHAGE IN DOGS IN RELATION TO AGE

AGE RANGE (YR.)	NUMBER OF ANIMALS	NUMBER WITH HEMORRHAGE	PERCENTAGE WITH HEMORRHAGE
1 to 3	31	6	19
3 to 5	36	17	47
5 and over	19	13	68

TABLE II. THE INFLUENCE OF ISOTONIC SALINE, EPINEPHRINE, AND PITRESSIN UPON HEART VALVE HEMORRHAGE IN DOGS

NUMBER OF ANIMALS	AGE RANGE (MONTHS)	DRUG TREATMENT	KILLED AFTER (DAYS)	NUMBER WITH HEMORRHAGE	PERCENTAGE WITH HEMORRHAGE
4	6 to 8	Saline*	1	0	0
1	5 to 6	Saline*	14	0	0
4	4 to 8	Epinephrine†	1	3	75
4	6 to 7	Epinephrine†	14	1	25
4	4 to 8	Pitressin‡	1	4	100
4	5 to 6	Pitressin‡	14	1	25
2	24 to 48	Saline*	0	2	100
10	18 to 48	Epinephrine†	1	8	80
2	24 to 48	Pitressin‡	0	2	100

*The intravenous injection of 0.5 c.c. of saline four times at two-hour intervals served as a control on the other experiments.

†Dose: 0.5 c.c. of 0.1 per cent epinephrine four times at two-hour intervals.

‡Dose: 0.5 c.c. of pitressin (Parke, Davis and Company) four times at two-hour intervals.

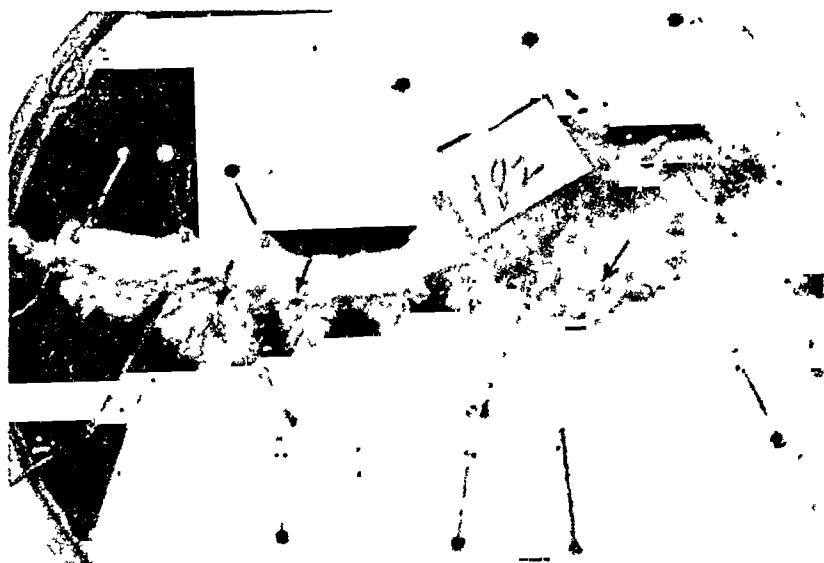


Fig. 1.—Gross appearance of the mitral valve of a dog showing hemorrhagic lesions at the points indicated by arrows.

on such lesions was studied first in dogs known to be less than 1 year old. Observations were made upon the effects of intravenous injections of 0.5 c.c. of 0.1 per cent adrenalin, repeated four times at two-hour intervals, with death of the animal either immediately, twenty-four hours, or two weeks later by intravenous potassium cyanide. Similar experiments were performed using the afore-mentioned doses of Pitressin (Parke, Davis Company). These experiments were controlled by giving equal quantities of isotonic saline to comparable numbers of animals of the same ages. The results appear in Table II in which it is evident that, when 5- to 8-month-old dogs are killed by potassium cyanide, after a control injection of saline, no subendothelial hemorrhages are seen. In the case of the 2- to 4-year-old dogs given saline, both showed hemorrhages. These observations are in confirmation of the results shown in Table I. The ten animals in the saline control series here were not included in Table I. If they are so added, the age difference shown in that table would be even more pronounced.

However, when either epinephrine or pitressin was given to young dogs killed within a day thereafter, hemorrhages appeared in 75 and 100 per cent of the animals, respectively. When death was delayed until two weeks after drug injection, hemorrhage was still evident in one dog out of four. With older

animals the incidence of hemorrhage with either drug was nearly 100 per cent, as might be expected. The important result is that after the employment of adrenalin and pitressin subendothelial hemorrhages were seen in young dogs which otherwise did not present such lesions.



Fig. 2.—Low-power view of a section of a mitral valve leaflet of a dog showing a large hemorrhagic area. Zenker-formalin fixation and hematoxylin-eosin staining (magnified $\times 30$).

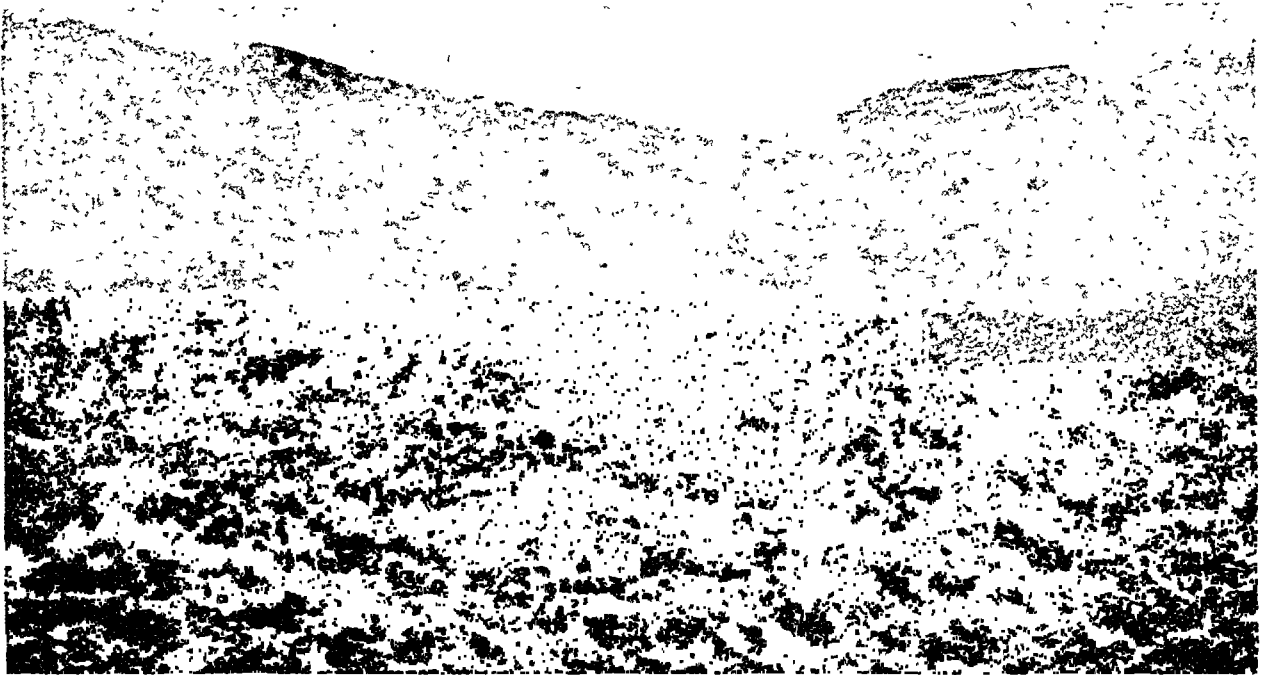


Fig. 3.—High-power view of a portion of the valve shown in Fig. 2 (magnified $\times 240$).

3. *Unsuccessful Attempts to Counteract the Hemorrhagic Effects of Epinephrine and Pitressin.*—Since ascorbic acid and vitamin P (citrin) have been shown to have an effect in preventing certain types of hemorrhage¹⁻³ it was thought desirable to test their effects upon the hemorrhagic effects of the two agents employed in these studies. Three series of experiments were performed. In the first, 500 mg. of ascorbic acid were administered daily for seven days, by capsule, before the vasospastic drug was given. In the second, the same doses of citrin were given. In the third, 150 to 200 c.c. of whole lemon water extract were given daily for fourteen to twenty-eight days by stomach tube. The lemon extract was prepared by placing forty-eight finely sliced lemons in a liter of water, boiling for ten minutes, macerating, cooling, filtering twice through gauze, and preserving on ice. This water extract contains both ascorbic acid and citrin besides other substances.

The results of these experiments are shown in Table III. Neither ascorbic acid nor citrin, in the doses used, exhibited any protective effect against

TABLE III. OBSERVATIONS ON ASCORBIC ACID AND CITRIN IN RELATION TO HEART VALVE HEMORRHAGE IN DOGS

NUMBER OF ANIMALS	AGE RANGE (MONTHS)	PRE-TREATMENT			DRUG TREATMENT	NUMBER WITH HEMORRHAGE	PERCENTAGE WITH HEMORRHAGE
		DRUG	DOSE PER DAY (MG.)	TIME (DAYS)			
2	2 to 3	Ascorbic acid	500	14	Saline*	0	0
2	2 to 3	Ascorbic acid	500	14	Epinephrine†	2	100
2	2 to 3	Ascorbic acid	500	14	Pitressin‡	2	100
2	3	Citrin	500	14	Saline*	0	0
2	3	Citrin	500	14	Epinephrine†	2	100
2	3	Citrin	500	14	Pitressin‡	1	50
4	8	Lemon extract	175	14	Epinephrine†	3	75
4	5 to 10	Lemon extract	175	21	Epinephrine†	3	75
4	6	Lemon extract	175	28	Epinephrine†	4	100
6	10	Lemon extract	175	18	Pitressin‡	5	83

*Dose: 0.5 c.c. four times at two-hour intervals one day before death with potassium cyanide.

†Dose: 0.5 c.c. of 0.1 per cent epinephrine four times at two-hour intervals one day before death with potassium cyanide.

‡Dose: 0.5 c.c. four times at two-hour intervals one day before death with potassium cyanide.

adrenaline, and an effect on the pitressin action is improbable; especially because nothing significant was seen with six dogs given lemon extract for eighteen days. It is concluded that ascorbic acid and citrin do not have a protective effect against adrenaline and pitressin when given in massive doses over a two- to four-week period.

In addition to the experiments outlined, studies were made on six dogs, 2 to 10 months of age, in which 10 to 20 mg. of papaverine per kilogram of body weight were administered subcutaneously from twenty to ninety minutes before each injection of epinephrine or pitressin in the usual doses. Of these six animals, five showed the characteristic hemorrhages. Thus, papaverine, which is an effective coronary dilator,⁴ did not, in the manner used, prevent the hemorrhagic effects of epinephrine and pitressin.

DISCUSSION

Nedzel^{5, 6} employed pitressin in studies on the production of bacterial endocarditis in dogs. He reported finding endothelial swelling following pitressin administration but did not mention the occurrence of subendothelial hemorrhage. He inferred that pitressin facilitated the production of experimental endocarditis. Dearing⁷ and Dearing et al.⁸ noted a high incidence of localized myocardial degeneration in cats treated with large doses of pitressin. They noted "small macroscopic reddish verrucae . . . in the mitral valves in some of the animals. Subendocardial hemorrhages were observed macroscopically in several animals. . . . The old animals (5 cats) were the only ones which developed myocardial lesions. Myocardial changes were not found in several young cats (4 animals)."

The lesions reported in this paper occurred with much smaller doses of pitressin than those reported by Dearing and his co-workers. He employed doses four to six times as great in cats as were used in this study in dogs. The relative sensitivity of the cat and dog to the actions in question may be different. No specific test of this question has been carried out. Nevertheless, it is interesting that young cats appeared to be more resistant to the hemorrhagic and myocardial degenerative effect of pitressin than are older animals.

The failure to prevent hemorrhages by ascorbic acid, citrin, and papaverine in these studies is not considered by the authors to have great significance. These agents were chosen for study because of their obvious relations, in the case of the first two, to small vessel hemorrhage, and in the case of the second, to

coronary constriction. In a systematic study of possible antagonists to this action of pitressin and epinephrine a much broader approach would be necessary. In fact it would be worth while, it is believed, to study the effects of the same agents under different conditions.

The experiments on attempted prevention of the hemorrhagic lesions are presented partly because they add to the proof that pitressin and epinephrine produce a high incidence of valve hemorrhage in young dogs. These observations can, without much doubt, be added legitimately to the data presented in Table II. If this is done one finds that, in sixteen dogs under 1 year of age given pitressin and killed within twenty-four hours, the incidence of valve lesions is 88 per cent. In the case of epinephrine the over-all incidence is also 88 per cent in twenty-four such dogs. This is in contrast to a zero incidence in twelve dogs under 1 year of age given control injections of saline. These figures are more impressive for statistical treatment than are those in Table II, alone. There can be no significant doubt about the reality of the pitressin and epinephrine effects in the light of the full data.

The frequent occurrence of valvular hemorrhage in routine autopsies on older animals requires discussion. It would be gratuitous to assume that the lesions seen after death were necessarily present before the animal was handled in any way. All animals were either anesthetized with ether or nembutal, or killed with intravenous potassium cyanide. In addition most of the anesthetized dogs were subjected to some experimental procedures, as indicated. None of the animals was specially "trained" for intravenous injection or other handling; therefore, it is likely that blood pressure elevation and vasomotor reactions occurred in most of the dogs during the several manipulations. It is still an open question whether death could be produced by any procedure which would not introduce some element of excitement, without an extensive training period. Furthermore, it would remain to be shown that any toxic substance employed as a lethal agent did not itself cause alterations in the blood vessels of the heart valves before it could be used to ascertain whether or not the valve hemorrhages existed before treatment.

Fortunately, the results here presented have some significance regardless of the precise mechanism of the development of lesions. The fact of the age difference in incidence is at once important because it demonstrates a defect in older animals as regards their ability to meet certain strains without damage. The fact that valve hemorrhages occur with such great frequency in older animals subjected to a variety of treatments suggests likewise that such lesions are likely to occur from time to time in the ordinary course of events in life. The excitement involved in anesthetization or intravenous injection of potassium cyanide under the careful conditions employed is probably not greater than that in many stress situations in life. Although we have no proof of the connection, it may be suggested that the roughened nodular valves seen with great frequency in autopsies of older humans, without rheumatic or bacterial endocarditis, could be the result of repeated hemorrhagic lesions of the type described here.

The greater frequency of occurrence of hemorrhagic lesions in older animals is also to be considered in connection with the age incidence of coronary vascular disease in the human. This is made more pertinent by the observations of Dearing on focal myocardial degeneration in cats. Both sets of observations point toward a greater susceptibility to damage under strain in older animals.

The present study obviously makes only a small beginning in the attack upon the problem. An exact physiologic analysis of the mechanism of produc-

tion of subendothelial hemorrhage is essential to further progress. It must be ascertained whether (1) blood pressure elevation, (2) extreme local ischemia with resulting injury to vessel walls, or (3) other factors, are responsible for the lesion. It will also be necessary to account for the fact that the mitral valves are the sites of predilection for hemorrhage. It occurs to one that mechanical trauma may be greatest at this point. Further, it will be necessary to ascertain whether (1) alterations in the condition of the vessels or (2) differences in the response to strain, are the cause of the differences in reaction at various ages. Such an analysis could scarcely fail to yield information important to an understanding of the ageing process. This preliminary report is being made in order to call attention to what are believed to be important facts basic to the entire problem.

SUMMARY

1. Observations on the state of the endocardium, particularly of the heart valves, have been made in one hundred seventy-eight dogs in relation to age, injection of pitressin and epinephrine, and in connection with attempts to prevent the occurrence of lesions following the use of such agents.

2. The incidence of subendothelial heart valve hemorrhages in routine autopsies on laboratory experimental animals was found to be more than three times as great in dogs over 5 years of age as in animals under 3 years.

3. In twelve dogs under 1 year of age the incidence of valve hemorrhage was zero after control injections of isotonic saline and death by intravenous potassium cyanide solution.

4. In sixteen dogs under 1 year of age given pitressin and killed within twenty-four hours the incidence of valve hemorrhage was 88 per cent. The same incidence was seen in twenty-four such animals given epinephrine.

5. Neither ascorbic acid, vitamin P, nor papaverine counteracted the hemorrhagic effects of pitressin or epinephrine, under the conditions employed.

6. These observations may provide a basis for an experimental approach to clinical problems related to age and cardiovascular diseases.

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ANGINA PECTORIS WITH PARTICULAR REFERENCE TO ITS OCCURRENCE BEFORE AND AFTER MYOCARDIAL INFARCTION

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IT IS the purpose of this article to present the results of an analysis of a large number of cases of chest pain of the kinds that suggest to the patient or his medical adviser that the heart is the source of the difficulty. It is not necessary to review here the classical picture of angina pectoris or to discuss at length the prevailing views as to the mechanism which gives rise to the characteristic symptoms. It is generally admitted that this syndrome is due to disease of the coronary arteries or to an absolute, or relative, deficiency in the quantity or quality of the blood circulating through the coronary system and the Thebesian vessels. Heberden¹ noted that many patients complained of pains in the chest which proved to be annoying but not serious and sharply differentiated between these and the disorder under consideration, which he was the first to describe. In practice, however, the differentiation between anginal pain and other less serious kinds of pain is not always easy. For the purposes of analysis, we have divided our cases of chest pain into the following groups:

A. Poorly Characterized Pains.—In this group we have placed cases of momentary stabbing pain without radiation; of indefinite pain lasting for hours and not related to effort; and of pain which lasted for a few minutes, did not radiate, and was influenced by respiration. We have also included, in this group, patients seen in consultation because of rheumatic, pleural, or neuralgic pain and those in which the pain was apparently of psychic origin. There are two kinds of chest pain of cardiovascular origin which fall into this group because they do not present features which make it possible to identify them with any certainty. We refer to the pain of aortitis, sometimes not severe, and usually located behind the sternum, which often comes on after, though not during, severe exertion and to the pain of pericarditis which is usually accompanied by fever and may simulate the pain of myocardial infarction, but usually does not radiate and is not associated with a feeling of oppression. Finally, we have included in this group, certain cases of pain occurring in women, without hypertension or diabetes, which simulated the pain of myocardial infarction closely but in which there were no associated changes in the electrocardiogram and there was no feeling of illness on the day afterward. We have seen a number of very interesting cases of this kind.

B. Angina of Rest.—In this group, we have placed cases of paroxysmal pain beneath the sternum or in the precordium, which occurred at rest and was not precipitated by an obvious factor, was of short duration, was accompanied in most instances by a feeling of oppression, was relieved by nitroglycerin, and radiated to one or both arms, to the neck, or to the jaws. We have not included here cases in which there was a history of myocardial infarction or in which the electrocardiogram displayed changes characteristic of infarction.

From the Cardiac Service of the Municipal Hospital, São Paulo, Brazil.
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TABLE I

Total number of cases analyzed	2,248
Pains not well characterized	429
Angina of rest (cases without history of infarction)	35
Angina of effort (cases without history of infarction)	46
Infarction	208

TABLE II

Angina of rest	Absence of signs	2
	Arteriosclerosis of the aorta	6
	Syphilitic aortitis	5
	Arteriosclerosis of the aorta and hypertension	3
	Arteriosclerosis of the aorta and mitral insufficiency	1
	Hypertension	4
	Coronary sclerosis	5
	Aortic insufficiency	1
	Aortic insufficiency and mitral lesion	2
	Mitral stenosis	3
	Congenital heart disease (pulmonary stenosis)	1
	Paroxysmal tachycardia	1
	Hyperthyroidism	1
Angina of effort	Absence of signs	4
	Arteriosclerosis of the aorta	3
	Syphilitic arteriosclerosis of the aorta	4
	Syphilitic aortitis and hypertension	3
	Arteriosclerosis of the aorta and hypertension	3
	Hypertension	5
	Hypertension and coronary sclerosis	7
	Coronary sclerosis	9
	Aortic insufficiency	5
	Aortic insufficiency and mitral stenosis	2
	Mitral stenosis	1

C. Angina of Effort.—In this group, we have placed cases in which pain of the type described in the preceding paragraph was induced by effort, emotion, the taking of food, or by exposure to cold wind. Here, also, we have excluded cases in which there was a history of infarction or in which the electrocardiogram was characteristic of infarction, although there were some cases in this group in which the electrocardiogram showed some of the features described by Wolferth in cases of lateral infarction.²

D. Myocardial Infarction.—We have placed in this group cases of anginal pain that was prolonged in the vast majority of cases and was accompanied by electrocardiographic changes that were characteristic of infarction from the first, or underwent the characteristic evolution.

The total number of case histories analyzed was 2,248; we placed 429 of these in the first group, 35 in the second, 46 in the third, and 208 in the fourth. The classification of the cases of angina of rest and angina of effort according to the type of heart disease present is shown in Table I. It will be noted that, of the 289 cases of anginal pain, there were 208 in which the pain was associated with infarction. The history of these cases of infarction showed that in most instances the patient experienced angina of rest or angina of effort, either before, or after, the coronary accident (Table II). Some patients had angina of effort and angina of rest simultaneously either before, or after, infarction occurred (Table III).

We found, then, a very high incidence of angina pectoris before or after infarction. Had our study been more complete, the incidence might have been still higher. Many of our observations on cases of infarction were relatively recent, and it was not possible to determine whether anginal pain would occur

TABLE III

Total number of cases of infarction	208
With angina of rest preceding the attack	66
With angina of effort preceding the attack	46
With angina of rest succeeding the attack	41
With angina of effort succeeding the attack	57

TABLE IV

Total number cases of infarction	208
With anginal manifestations pre or post infarction	137
Without anginal manifestations pre or post infarction	71

when the patient returned to a more or less normal life. It is also probable that infarction had occurred in some of the cases classified as angina of effort but could not be diagnosed because the electrocardiographic changes due to infarction had disappeared and the history did not give the necessary information. It will be noted that angina of rest preceded infarction frequently. It is possible that its frequency after infarction is less than our tables indicate. In some instances, the attacks of pain considered angina of rest may have been induced by some factor that was not noted. There were also some cases classified as angina of rest in which the patient had a series of attacks of pain separated by short intervals; these may have represented the gradual development of an infarct or a series of minor coronary accidents. Judging by those cases, which were under observation for a long period, angina of rest after recovery from infarction is infrequent.

Angina of effort after infarction is much more common. This type of angina occurs under other circumstances (in syphilitic aortitis, in mitral or aortic stenosis, in hypertension, in anemia, and in hyperthyroidism) when there is a deficient flow of blood through the coronary arteries during strenuous exertion. But the incidence of angina of effort in these conditions is small in relation to the number of cases in which it precedes or follows myocardial infarction, and the disparity would be greater if more information concerning the subsequent history of patients seen in consultation were available and more extensive electrocardiographic studies had been carried out during periods following the more severe and prolonged attacks of pain.

We are aware that our views concerning the relation of angina pectoris to infarction are not in accord with those held in many medical centers. We may point out that, if syphilitic aortitis were a common cause of angina pectoris, one would expect to encounter in Brazil, where syphilis is a very common disease, many cases of anginal pain due to syphilitic narrowing of the coronary orifices. In our experience, however, cases of this kind are rare in comparison to the number of cases of anginal pain before or after infarction.

Our observations on the close relation between infarction and angina pectoris have led us to investigate cases of this disorder with considerable care. The prognosis and the treatment must be based, first of all, upon a detailed and carefully taken history. When the history is taken by one who is very familiar with the symptomatology and conscious of the importance of details, it provides information that cannot be obtained in any other way.

Usually, angina of rest and angina of effort can be easily differentiated. The former is spontaneous and paroxysmal, but it is not always intense. The discomfort is usually located beneath the sternum, in the precordium, or in the epigastrium, and often radiates to the arm. It is sometimes felt in the shoulders,

elbow, or wrist, and, when this is the case, it is not influenced by movement of the joints of the extremity affected. Angina of rest is very frequently followed by infarction, and this is probably why it has been considered one of the most serious of cardiac symptoms. Whenever a diagnosis of angina of rest is made, and whenever the history suggests that it may be present, we advise the patient to be extremely careful. We often take this precaution in cases where there has been rather indefinite pain, or painful discomfort, of brief duration beneath the sternum, in the precordium, or in the shoulders or arms. It is clear that there is a great possibility of error in diagnosis in such cases, but to learn that a patient who has been told that his discomfort is of no consequence and has been reassured has died soon afterward from a coronary occlusion is a very disagreeable experience which we, like most physicians, wish to avoid.

Some patients with typical angina of rest, before or after the occurrence of infarction, have rather prolonged crises at frequent intervals, as if there were a succession of minor infarctions. In some of these cases, the form of the electrocardiogram varies from one attack to another. The occurrence of sudden death after a series of such anginal attacks or the development of characteristic electrocardiographic changes strongly suggests that a series of small infarctions ended in a major one.

In angina of effort, the diagnosis is easier, but it should be remembered that the location of the pain is quite variable; it may be in the wrist, elbow, neck, epigastrium, or right upper quadrant of the abdomen, rather than beneath the sternum. We believe that pain in the thorax or upper abdomen, which is clearly precipitated by effort, is due to coronary insufficiency in all except very rare cases. Angina of effort which precedes infarction often displays a rapid increase in severity which enables us to foresee the outcome: the patient complains that he has been having the pain for weeks or months, but that every day he feels worse and develops pain after less exertion. There are, however, curious cases in which the effect of effort is very variable.

In the case of syphilitic aortitis with narrowing of the coronary orifices, and in aortic insufficiency, angina of effort usually evolves slowly, often over a period of years.

Angina of effort after infarction is more frequent than angina of effort before infarction. We believe that the former would be still more common if it were not customary to keep the patient at rest for a long period following the coronary accident. It is logical to suppose that a seriously injured heart will not tolerate the strain imposed by effort without producing unfavorable reactions. There are, however, occasional cases of recent infarction in which exertion does not produce pain. The occurrence of cardiac pain, like the occurrence of pain of other types, is determined to some extent by psychic factors; this probably explains why, after a coronary accident, some patients complain of pain which is sometimes vague and at other times more intense and does not seem to be closely related to the work imposed upon the heart. In such cases, it is often difficult to know whether the pain should be attributed directly to the infarction, to disturbances in coronary circulation due to emotional reactions, or to purely psychic causes.

Arthritic symptoms are not uncommon after infarction and sometimes develop several months after a coronary accident. The shoulder is the joint most often involved and the pain is closely related to movement of the arm, which clearly indicates that it is not anginal.³

When angina of effort does not appear during convalescence from myocardial infarction, under circumstances which commonly induce it, and dyspnea is also absent, the prognosis is naturally favorable. The prognosis is also favorable when, as often happens, angina of effort does occur in the earlier stages of convalescence but becomes less frequent and requires more effort to induce it as time goes on and, eventually, disappears. This is particularly true when no enlargement of the heart takes place.

It is interesting that angina of rest of short duration is rare after infarction. In contrast to the situation that obtains before infarction, we can almost always ascertain what the provoking factors are when anginal pain occurs after infarction: physical effort, emotion, reflexes, or other effects associated with digestion.

SUMMARY

Angina of rest and angina of effort may occur under a great variety of circumstances, but in the vast majority of cases they precede or follow myocardial infarction. In syphilitic aortitis and diseases other than those which lead to myocardial anorexia by direct involvement of the coronary arteries, angina pectoris is, by comparison, infrequent.

Angina pectoris is usually more severe when it precedes, than when it follows, infarction: and angina of rest is very much more common before, than after, infarction has occurred, particularly if we exclude from this category the pains separated by short intervals that sometimes accompany the crisis. When anginal pain following infarction is not related to exertion, it is often due to other precipitating factors and the diagnosis of angina of rest, if this is defined as spontaneous anginal pain, is difficult.

Angina of effort, which displays a rapid increase in severity and requires less and less effort to induce it, suggests that infarction is imminent. After infarction, the absence of angina of effort or a progressive decrease in its severity is a favorable omen. In such cases, we believe that a gradual increase in the patient's physical activity is beneficial.

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FACTS AND FALLACIES ABOUT THE NORMAL APEX BEAT

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PALPATION of the precordium in health and disease is a valuable diagnostic procedure. The location of the apex beat gives first rate evidence regarding the size of the heart. It furnishes evidence of the size of the heart as valuable as that shown by fluoroscopy. When demonstrable, it is a more valuable sign of the heart size than roentgenograms, as usually taken, in full inspiration.

On reviewing the information regarding the apex beat presented in the textbooks of physical diagnosis and cardiology, one is struck by the uncritical discussions of this subject. This is evident in the following excerpts: Paul D. White¹ in regard to locating the apex beats, states, "This is possible in the majority of cases, failing only in a few obese or very sick patients." Norris and Landis² in discussing the cardiac impulse, observed that the intensity depends on "(a) rapidity and the force of the ventricular contraction, (b) the shape of the chest, (c) the amount and the character of the overlying soft tissue . . . in deep chested or corpulent individuals . . . may be imperceptible." (Sutton³ states: "Apex beat is the forceful projection of the apex against the chest wall." "Force varies widely in different individuals." "When the apex beat cannot be felt, leaning the body forward may make it more readily palpable." Pratt and Bushnell⁴ state: "Up to the twentieth year the cardiac impulse can be felt in practically every chest in health. With increasing age it can be less readily palpated, and by age fifty it can be felt in about forty per cent of the people. In old age it becomes again more frequently palpable." Cabot and Adams⁵ state that the apex impulse is visible in most persons. "More accurate localization of the maximum impulse, than is possible by inspection, can often be made by palpation." Alfred L. Loomis⁶ writes: "The cardiac impulse is visible in the majority of persons." "Palpation determines the force of the cardiac pulsation." Sahli⁷ states, "An impulse synchronous with the heart action . . . can be felt over the precordia of healthy individuals." Majors,⁸ in discussing points of maximum impulse, says, "This is normally located in about the fifth costal interspace inside the mamillary line." He also quotes William Harvey in *De Motu Cordis*, "The heart is lifted and rises up to the apex, so that it strikes the chest wall at that moment and the beat may be felt on the outside." Sterns⁹ says, "The apex can generally be located (by palpation)."

Elias states,¹⁰ "Apex Beat" . . . "Normally palpable in the 4th or 5th interspace, but may not be." Selective Service Regulations¹¹ require "Location and determination of the character of the apex impulse." Elmer and Rose¹² write, "In normal subjects the point of maximum intensity of impulse is seen in the fifth intercostal space just inside the midclavicular line." Anderson¹³ writes, "Though usually found in the left fifth intercostal space within the nipple line, it is subject to change even in a normal chest." Hope¹⁴ says, "The apex beats between the cartilages of the fifth and the sixth left ribs at a point about two inches below the nipple, and one inch on its sternal side."

¹ From the Department of Internal Medicine, University of Nebraska, College of Medicine, Omaha, Nebraska.

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From these quotations it is apparent that the subject is treated in generalities. The impression is invariably left that the apex is normally always present, having features identifying it as easily as the "nose on the face." Dressler¹⁵ seems to be the only exception to this point of view. In his presentation on pulsations of the chest wall he discusses the subject as follows:

"The apex beat is the most prominent pulsatory phenomenon caused by the contraction of the normal heart. This is a circumscribed systolic elevation, one to two centimeters in width, felt at, or somewhat inside of the midclavicular line in the fifth interspace in adults. The apex beat is usually well developed in children, becoming less distinct between ages of twenty to thirty years. In adults over thirty years a visible or palpable apex beat, noted in the recumbent position, should arouse suspicion that some pathological condition is present.

"The 'point of maximum intensity' may not always be synonymous with the 'apex beat,' as in various pathological conditions a powerful forward thrust is caused by segments of the heart quite distant from the apical area."

For many years it has seemed to us that the apex beat was absent more often than present. In doing insurance examinations, it seemed a bit compromising with the truth when it was necessary to describe the character and locate the apex beat in all individuals, usually spotting it accurately on an anatomic diagram (Fig. 1).

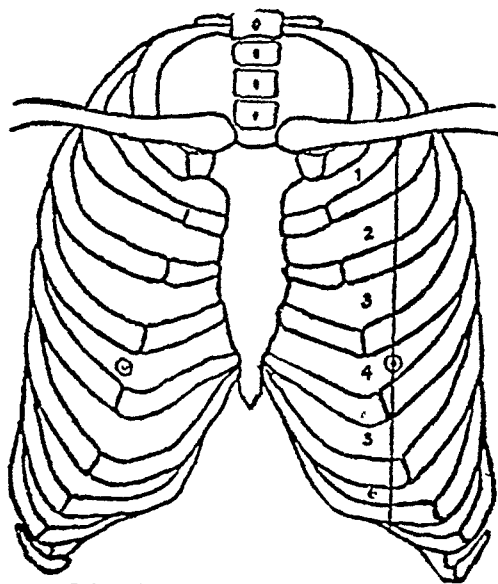


Fig. 1.—Anatomic diagram.

METHOD

It was apparent that all apex beats were not equally visible or palpable, so a simple system of grading was conceived:

Apex Beat (point of maximum intensity in normal hearts).—Grades (indicating its absence or its degree of presence):

0. Complete absence of any suggestion of a pulsation, at or near, the apical region.
1. Some pulsation, but indefinite; cannot be used as an indication of the location of the apex beat or the size of the heart.
2. Apex can be located; it may be faint, but it is definite. It may be only visible, or palpable, or both. It may be present only in the erect, prone, or leaning forward position, or in all positions.
3. Apex beat definitely palpable and usually visible. Typical "nose on the face" type.

Cardiac Impulse.—

This refers to any pulsation caused by the heart in the precordium with, or without, an apex beat.

The relation of the heart to the exterior surface of the precordium has been referred to, by the term, "heart accessibility." Factors influencing this situation are (1) the thickness of the chest wall, due to bones, muscle, and fat (in women the mammary gland), (2) the contour of the chest, least favorable in the barrel type, and (3) lung distention, fully developed in emphysema. These factors are not sufficiently emphasized in teaching students or appreciated by practitioners.

In order to obtain some definite information, it was decided to record the results of palpation of normal hearts. All cases of cardiac disease were excluded. These findings were recorded as a part of regular physical examinations. The precordium was inspected in good light. In women the breasts were lifted. Both inspection and palpation were done in the erect and the recumbent position and, if negative, in the leaning forward position. Time consuming procedures were purposely avoided. It was estimated that not more than thirty seconds were added to the time for examination. The apex beat was graded and recorded according to the previous classification. The cardiac impulse was recorded as to whether it was absent or present, but the intensity of the impulse was not graded.

The precordia of 1,000 persons with apparently normal hearts were inspected and palpated. The results were recorded, as indicated previously. These were analyzed as follows: (1) How frequently can the apex be located definitely by inspection and palpation? (2) How frequently can the apex be located with sufficient accuracy to be used as an indication of the size of the heart? (3) What is the influence of age on the demonstrability of the apex beat? (4) How does body weight influence the demonstrability of the apex beat?

RESULTS

It became apparent, early in this study, that little was gained by grading the intensity of the apex beat beyond definitely establishing its absence or presence. However, grading into four degrees was continued during the whole study. It did stimulate greater scrutiny and, for this reason, should be continued for a system of grading.

The important facts regarding the absence or presence of the apex beat can be better studied by combining Grade 0 and Grade 1 as the nonapparent type, since neither of these grades locate the apex beat or furnish any evidence of the size of the heart, and combining Grades 2 and 3 as the apparent type, both of which give first class evidence of the size of the heart.

Fig. 2 shows the incidence of combined apparent and nonapparent apex beats in males and females according to age. It is strikingly evident that, after 20 years of age, the apex beat becomes less demonstrable. This is less evident in women than in men but occurs in both sexes. Up to 20 years of age, the apex can be distinctly felt in 54 per cent of males and 55 per cent of females; between 20 and 30 years of age it drops to 27 per cent of males and 39 per cent of females. This progressive decline is graphically shown in the chart.

Fig. 3 shows the incidence of the apparent and nonapparent apex beats as influenced by the body weight. Weight is a very important factor in the accessibility of the heart and in the demonstrability of the apex beat. Again, the apex beat is more frequently demonstrable in females. In the weight range from 100 to 120 pounds the apex beat is a distinct sign in 45 per cent of males and 46.8 per cent of females. With increase of the body weight the demonstrability of the apex beat rapidly decreases, somewhat faster in the males than in the females.

The overall demonstrability of the apex beat is shown in Table I according to age, showing a definite apex beat absent in 76 per cent (Grade 0, 56 per cent; Grade 1, 20 per cent) and present in 24 per cent (Grade 2, 10 per cent; Grade 3, 14 per cent) of normal individuals.

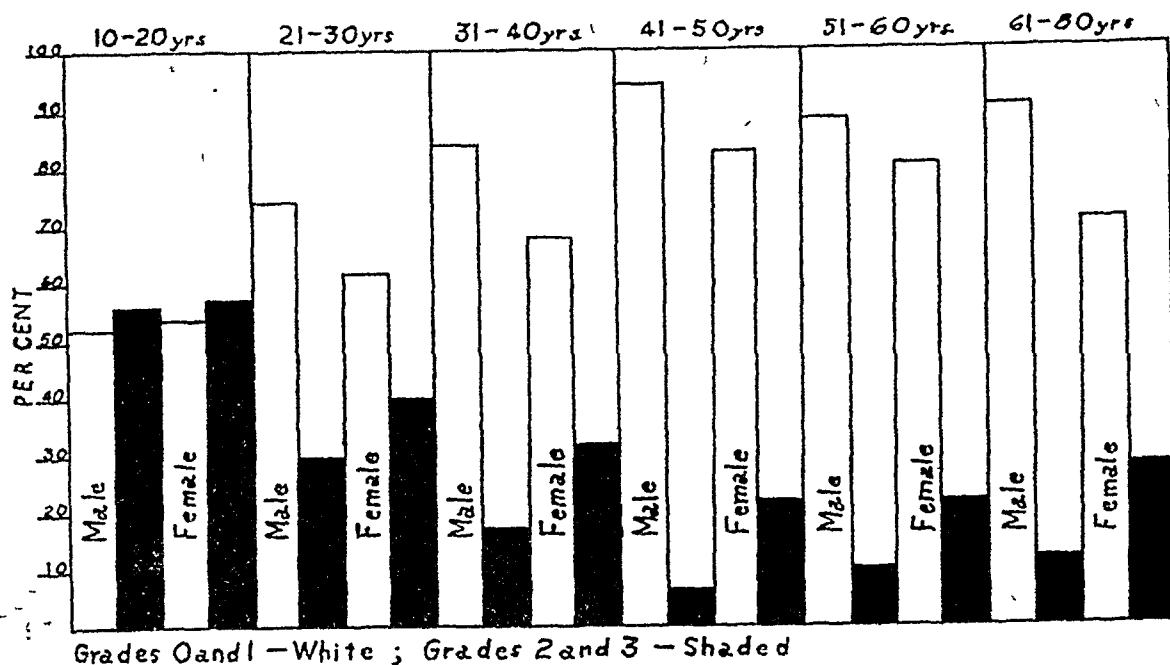


Fig. 2.—Apparentness of the apex beat according to age and sex.

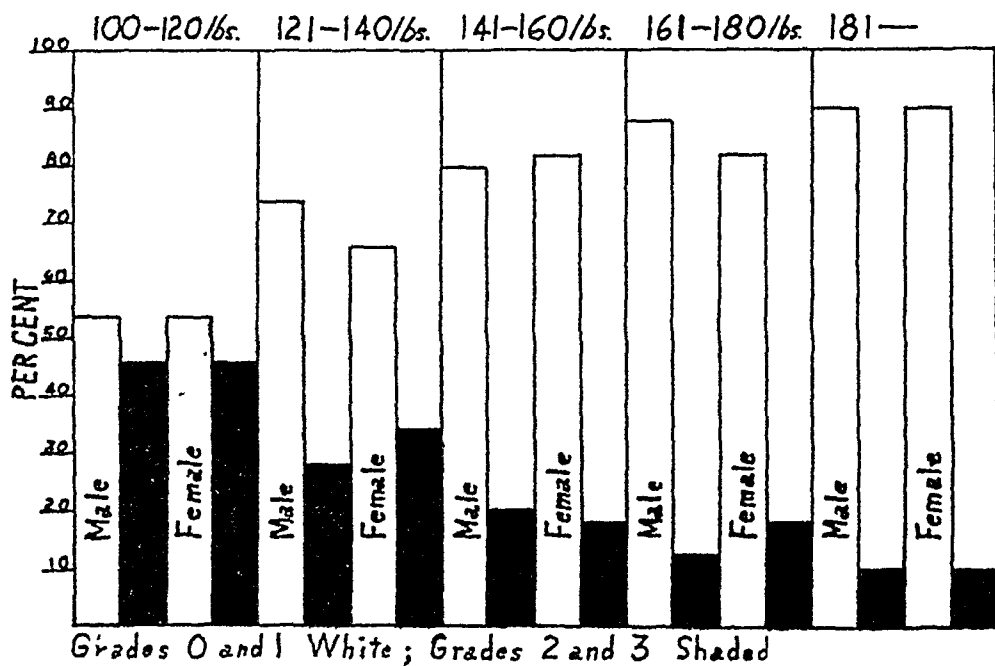


Fig. 3.—Apparentness of the apex beat according to body weight and sex.

Table II shows the same relation according to weight. In 74.8 per cent (Grade 0, 54 per cent; Grade 1, 20.8 per cent) of subjects the apex beat was absent. In 25.1 per cent (Grade 2, 10.8 per cent; Grade 3, 14.3 per cent) it was demonstrable.

Tables III and IV show the actual numbers of individuals studied and the percentage in each group according to age. Tables V and VI show the same relation for individuals according to weight.

CONCLUSIONS

1. Critical inspection and palpation of the precordia of 1,000 normal persons reveal the fallacies in the teachings regarding the normal apex beat.

TABLE I. ALL AGES

SEX	APEX BEAT								CARDIAC IMPULSE			
	0		1		2		3		ABSENT		PRESENT	
	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
Male	336	67.7	77	16	33	6.5	49	9.8	414	83.6	81	16.4
Female	224	44.3	123	24.3	67	13.3	91	18	357	70.5	148	28.5
Total	560	56	200	20	100	10	140	14	771	77	229	23

TABLE II. ALL WEIGHTS

SEX	APEX BEAT								CARDIAC IMPULSE			
	0		1		2		3		ABSENT		PRESENT	
	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
Male	332	67	79	16	32	6.5	52	10.5	404	81.6	91	18.4
Female	209	41.4	129	25.6	76	15	91	18	353	70	152	30
Total	541	54	208	20.8	108	10.8	143	14.3	757	75.7	243	24.3

TABLE III. AGE GROUP OF MALES

AGE (YRS.)	APEX BEAT								CARDIAC IMPULSE			
	0		1		2		3		ABSENT		PRESENT	
	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
10-20	14	28	9	18	9	18	18	36	24	48	26	52
21-30	29	45.9	17	72.1	7	11	10	16	47	74.6	16	25.4
31-40	60	63.8	18	19.2	7	7.5	9	9.5	77	82	17	18
41-50	94	83.2	13	11.5	2	1.8	4	3.5	102	90	11	10
51-60	71	80	10	11	4	4.5	4	4.5	83	93	6	17
61-80	68	80	10	10.8	4	4.6	4	4.6	81	94	5	6

TABLE IV. AGE GROUP OF FEMALES

AGE (YRS.)	APEX BEAT								CARDIAC IMPULSE			
	0		1		2		3		ABSENT		PRESENT	
	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
10-20	15	21.2	24	33.8	10	14	22	31	38	53.5	33	46.5
21-30	35	31.8	32	29.1	15	13.6	28	25.5	60	54.5	60	45.5
31-40	39	42	24	25.7	18	19.3	12	13	74	79	19	21
41-50	54	61.3	15	17.3	8	9	11	12.4	73	82.9	15	17.1
51-60	52	60	17	20	8	9	10	11	67	77	20	23
61-80	29	51.6	11	20	8	14.2	8	12.2	45	80.3	11	19.7

TABLE V. WEIGHT GROUPS OF MALES

WEIGHT (LBS.)	APEX BEAT								CARDIAC IMPULSE			
	0		1		2		3		ABSENT		PRESENT	
	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
100-120	5	25	6	30	4	20	5	25	9	45	11	55
121-140	32	45.9	19	27	6	8.6	13	18.5	46	65.7	24	34.3
141-160	100	60.3	34	20.5	16	9.6	16	9.6	129	77.7	37	22.3
161-180	105	78.3	14	10.5	5	3.7	10	7.5	123	91.8	11	8.2
180-	90	85.7	6	5.8	1	0.9	8	7.6	97	92.4	8	7.6

TABLE VI. WEIGHT GROUPS OF FEMALES

WEIGHT (LBS.)	APEX BEAT								CARDIAC IMPULSE			
	0		1		2		3		ABSENT		PRESENT	
	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
100-120	88	20.7	61	33.2	35	19.1	50	27	101	54.9	83	45.1
121-140	58	37.2	45	28.9	24	15.4	29	18.5	108	69.2	48	30.8
141-160	53	63.9	14	16.9	8	9.6	8	9.6	73	88	10	12
161-180	41	68.4	8	13.4	7	11.6	4	6.6	50	83.3	10	16.7
181+	19	86.5	1	4.2	2	9.3	0	0	21	95.4	1	4.6

2. The overall demonstrability of the apex for all ages and weights, and both sexes, is only 24.6 per cent instead of the implied 100 per cent.

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Clinical Reports

PERIARTERITIS NODOSA

REPORT OF CASE

CAPTAIN JOHN C. EAGAN, M.C.

BECAUSE of the recent interest in periarteritis nodosa and the striking features in this case, the following report is presented:

CASE REPORT

A married white man, aged 37 years, was admitted to the Station Hospital, Fort Snelling, Minnesota, March 6, 1944, complaining of a pain in the left side of the chest, nonproductive cough, backache, fever, muscle aching, and stiffness of leg muscles. The past history was negative. The patient denied infection with venereal disease. The family history was negative except for the fact that his father died at the age of 70 years from arteriosclerosis.

The patient stated that he had been sick with a cold for a week prior to his admission to the hospital. During this period he had perspired freely at night. At the time of admission, the patient complained of a pain throughout the left side of his chest, dry nonproductive cough, backache over the renal area, and extremely painful arm and leg muscles which he described as being stiff. Any movement of the muscles gave him considerable discomfort. He complained of feeling extremely tired and weak.

Physical examination revealed a temperature of 100° F., pulse rate, 96 per minute; respirations, 20. The breath sounds were increased throughout the left side of the chest and a few scattered râles were heard throughout the left side of the chest, posteriorly. The blood pressure measured 106/70. The examination of the heart was negative. There was tenderness of the forearm and the calf muscles. A roentgenogram of the chest taken March 9, 1944, showed no abnormalities in the lungs.

Laboratory examination showed 12,550 leucocytes per cubic millimeter; hemoglobin (Sahli) 89 per cent; neutrophils, 70 per cent; lymphocytes, 28 per cent and eosinophiles, 2 per cent. The urine specific gravity was 1.020, with an acid reaction. It was negative for albumin and sugar. The sediment was normal. The blood Kahn was negative. The sedimentation rate of the blood was 50 mm. in one hour.

A tentative diagnosis was made of rheumatoid state or influenza.

On March 22, 1944, the patient continued to complain of extreme weakness of the leg muscles and he also complained of substernal pain. The temperature curve was irregular with variations from 100° to 102.6° F. The pulse rate was 90 to 100. The patient became constipated and required the use of laxatives and enemas. He stated that he did not have strength enough to move his bowels. The weakness became more marked. Blood cultures were taken and reported as negative. Blood counts showed 4,500,000 erythrocytes per cubic millimeter, 17,900 leucocytes per cubic millimeter, and hemoglobin (Sahli) 85 per cent. The differential blood count was reported as neutrophils, 82 per cent; lymphocytes, 17 per cent; eosinophiles, 1 per cent.

On March 27, 1944, after a trial of salicylates with no apparent results, sulfadiazine was administered. No effect was noted on either the patient's well-being nor the fever.

On March 29, 1944, the test for heterophile antibodies was negative. There were no agglutinins for typhoid, paratyphoid, tularemia, or undulant fever in the blood serum. The blood serum proteins were: total, 5.65 Gm.; albumin, 3.59 Gm.; globulin, 2.06 Gm. per 100 cubic centimeters. The spinal fluid was clear, with 2 leucocytes per cubic millimeter; sugar, 61 mg. per cent. The Wassermann test was negative, and the colloidal gold curve was reported as 0000000. The test for globulin was negative.

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On March 31, 1944, the leucocyte count was 21,250 per cubic millimeter. The hemoglobin was 85 per cent (Sahli). The neutrophils were 92 per cent and the lymphocytes were 8 per cent.

Repeated sputum examinations were negative for tubercle bacilli and *Monilia*. A stereogram of the chest on April 3, 1944, showed a decreased radiolucency in the right lower lung field in the region of the cardiohepatic angle which extended out from the lower portion of the right hilum to the costophrenic angle, suggestive of early pneumonitis. The heart was more transverse and appeared to be somewhat larger, both to the right and to the left. The transverse diameter of the heart was 16.2 centimeters. The transverse diameter of the chest was 32.7 centimeters.

On April 3, 1944, all sulfonamide therapy was stopped and 10 Gm. of sodium salicylate were given intravenously. The patient noted a marked ringing in his ears but seemed to obtain considerable relief. He stated that he felt much better and could raise his arms and legs without pain. Sodium salicylate, 160 grains, was given each day. The electrocardiographic findings were: auricular rate, 120 per minute; ventricular rate, 120 per minute; regular rhythm; P-R interval 0.20 second; QRS interval, 0.06 second; R-T interval, 0.24 second. Impression: sinus tachycardia.

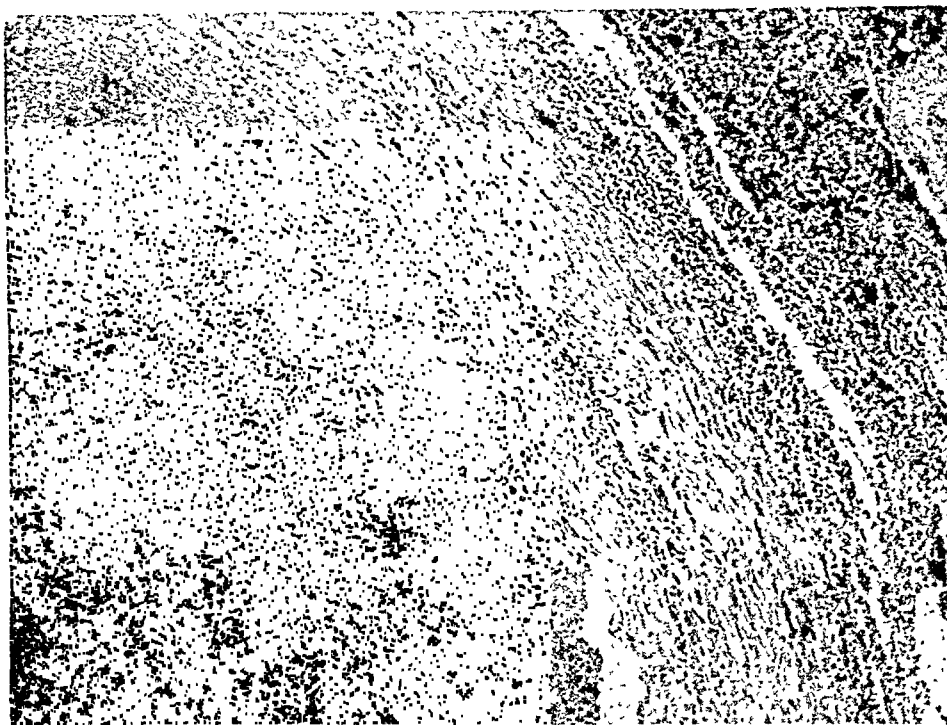


Fig. 1.—Wall of a coronary artery showing a thrombus in the lumen with massive periarterial exudate and thinning, resulting in destruction of the wall of the artery. (Magnification, $\times 100$; hematoxylin-eosin stain.)

On April 9, 1944, the patient noticed a numbness and tingling in the ulnar distribution of the right forearm and hand. A marked weakness of the right arm was also noted. He stated that he was unable to raise his right or left arm. The patient had been losing weight rapidly and had been unable to rest at night. Vitamin B₁ was given parenterally.

On April 15, 1944, an enlarged, extremely tender node was found in the right axilla. Several small nodular masses were noted along the lateral margin of the right tibia; these seemed to be attached to the vessel. The clinical diagnosis was changed to periarteritis nodosa.

A nodule was removed and sent to the Department of Pathology of the University of Minnesota. The pathologist confirmed the diagnosis of periarteritis nodosa from the biopsied nodule.

On April 25, 1944, weakness and numbness were noted in the left forearm and hand. There was progressive loss of weight. More nodules were noted in the left arm. Penicillin therapy was started by intravenous route and continued intramuscularly. On April 30, 1944, the patient suddenly complained of a headache and could see only large objects; he became comatose. The reflexes on the left side were diminished; the reflexes on the right side were exaggerated. The clinical impression was probable involvement of a cerebral vessel or uremia. The patient had several convulsive seizures and became very

cyanotic. Urinalysis was negative. The fluid intake was accomplished by administration of fluids intravenously. On May 2, 1944, little change was noted except an inability to respond to questions. On May 3, 1944, he seemed more alert, the vision was clearer, and he was able to recognize both objects and people. About midday he started to hiccup, cyanosis developed, the breathing ceased, the head dropped to the left, and the patient expired on the fifty-eighth day of hospitalization.

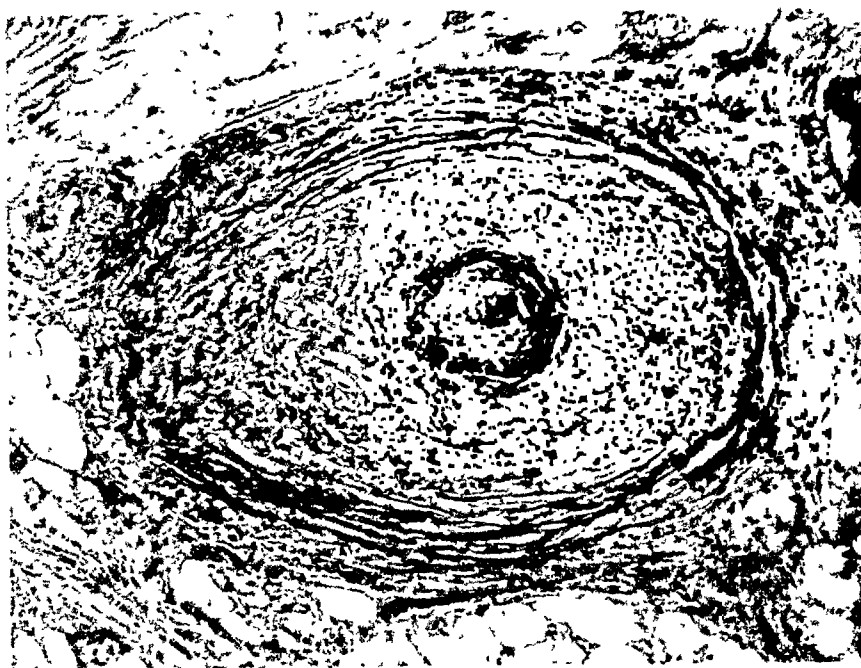


Fig. 2.—Artery of the cutis showing marked thickening of the intima with characteristic band of hyaline near the lumen and cellular exudate throughout all layers of the artery. (Magnification, $\times 65$; hematoxylin-eosin stain.)

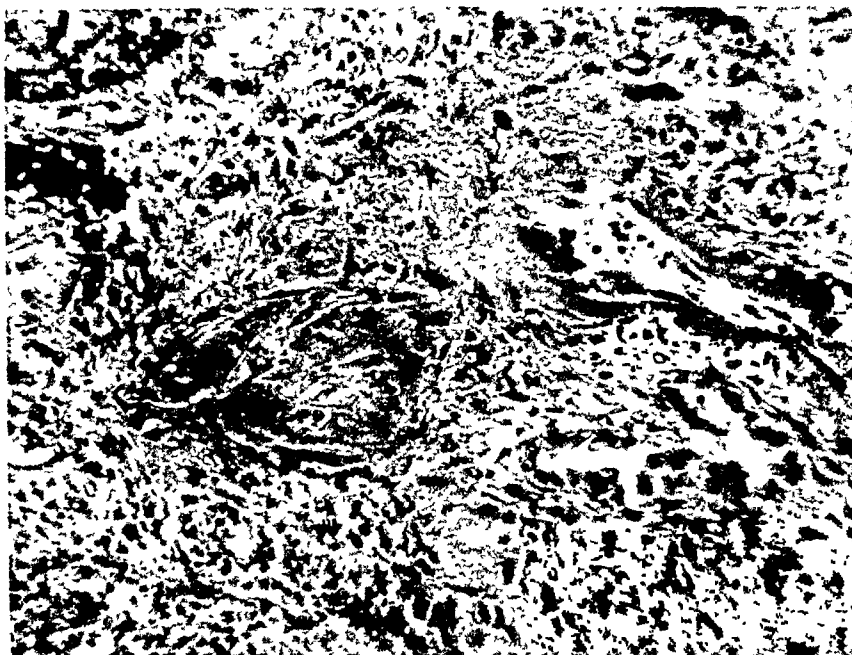


Fig. 3.—An artery in the kidney showing characteristic hyaline degeneration of the intima and a moderate amount of inflammatory exudate in the adventitia. (Magnification, $\times 150$; hematoxylin-eosin stain.)

NECROPSY FINDINGS

Subconjunctival petechiae were present in the conjunctiva of the right eye. The pericardial sac contained an increased amount of fluid. The heart weighed 475 grams. There was left ventricular hypertrophy. The anterior descending branch of the left coronary artery was partially occluded in its proximal third by a thrombus (Fig. 1). The spleen

weighed 300 grams. There was thrombosis of the splenic vein. Multiple infarcts were found in the spleen. An artery of the cutis, taken from the abdominal wall, showed marked thickening of the intima with a characteristic band of hyaline near the lumen, and cellular exudate throughout all layers of the artery (Fig. 2).

Liver: Weight, 2,350 grams. Numerous small aneurysms were found in the intra-hepatic arteries.

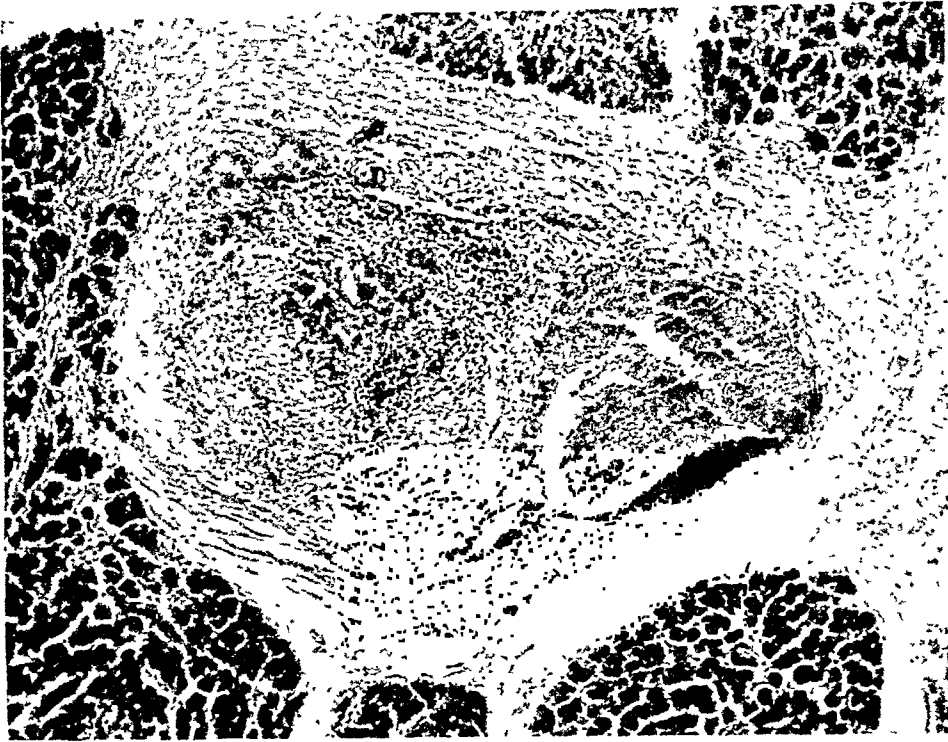


Fig. 4.—An artery in the pancreas showing inflammation in the artery with exudate from lumen to adventitia. (Magnification, $\times 65$; hematoxylin-eosin stain.)

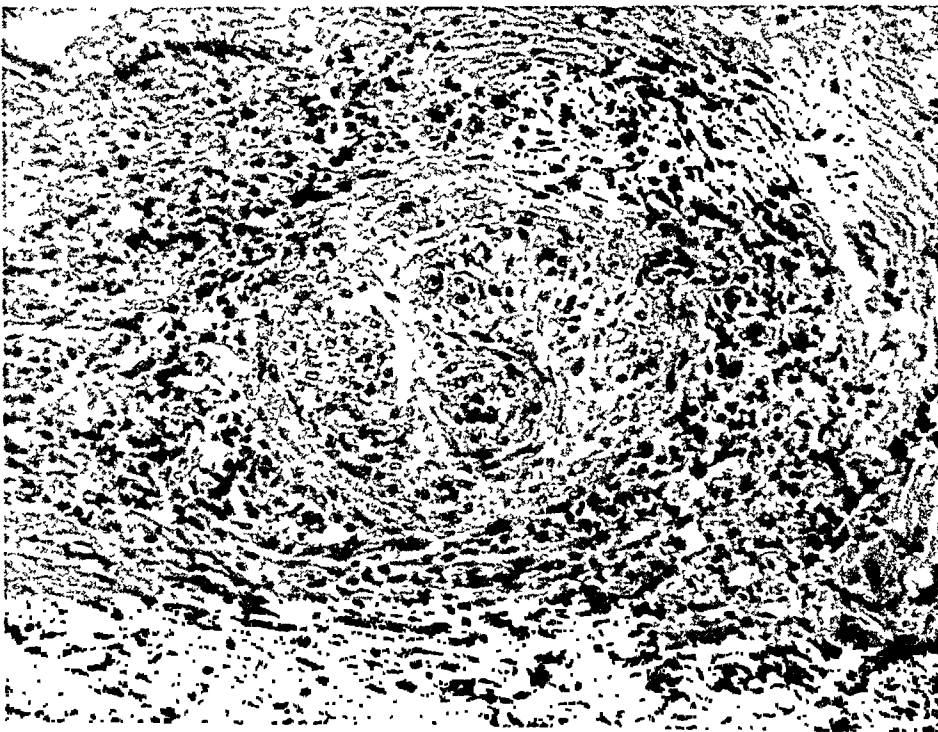


Fig. 5.—A small artery showing massive periarterial exudate and an organized thrombus in the intima. (Magnification, $\times 150$; hematoxylin-eosin stain.)

Gastrointestinal tract: A superficial ulcer was found on the lesser curvature of the stomach. A small aneurysm was noted in the mesenteric artery supplying the jejunum.

Kidneys: The right weighed 225 grams; the left weighed 250 grams. Both kidneys showed sunken areas on their surfaces. The centers were pale and the margins were hemorrhagic. There were subcapsular petechiae in both kidneys. Petechial hemorrhages were present in the pelvis of the right kidney (Fig. 3). An artery in the pancreas showed

inflammation with exudate spread from the lumen through to the adventitia (Fig. 4). A small artery showed massive periarterial exudate and an organized thrombus in the intima (Fig. 5). Several enlarged periaortic lymph nodes in the region of the common duct were found. Subperiosteal petechiae were found on the calvarium.

COMMENT

According to Bell¹ periarteritis nodosa is an inflammatory lesion affecting the medium-sized and small arteries in various parts of the body. The anatomic feature is the presence of the nodular thickenings of the arteries which represent small thrombosed aneurysms. Nodules are most easily observed on the coronary and mesenteric vessels; usually they are only a few millimeters in diameter and appear as firm, rounded, whitish masses, separated by segments of normal artery.

The initial lesion seems to be an injury of the media with the formation of hyaline necrotic tissue. This is soon followed by cellular infiltration of the walls with mononuclear leucocytes, eosinophiles and polymorphonuclear leucocytes. The infiltrate fills the adventitia of the vessel and may spread into the surrounding tissue. The small vessels usually become thrombosed. A weakening of the wall leads to the formation of a small aneurysm which usually becomes thrombosed, but may rupture. Small infarcts found in the kidneys cause renal insufficiency. Frequent abdominal pain is probably due to a closure of a mesenteric vessel. According to Bell¹ the cause of death may be uremia, hemorrhage, coronary thrombosis, or a cerebral accident.

Landis² describes periarteritis nodosa as a form of panarteritis accompanied by systemic symptoms of infection with added regional symptoms, depending on the organs involved. The specific agent is unknown, but suggested causes are streptococci, a filtrable virus, or allergy. Landis described a typical case with the onset being either insidious or violent with moderate fever, sweating, tachycardia, malaise, fleeting edema, progressive weakness, and accompanying diffuse, joint, muscular, or abdominal pain. There is secondary anemia with moderate to severe leucocytosis and, occasionally, conspicuous eosinophilia. The liver and spleen may be palpable. The muscles are usually atrophied and tender. The blood pressure may be elevated. In contrast to thromboangiitis obliterans, the visceral arteries are more frequently affected than the peripheral arteries.

Lichtman et al.³ state that the possibility of periarteritis nodosa should be considered in young adults who present a picture of a febrile, very debilitating disease that may have an occasional exacerbation, with pain in the abdomen and extremities, anemia, albuminuria and hematuria, peripheral neuritis, loss of weight and with subcutaneous nodules.

The bizarre picture should place one on his guard, and by a process of elimination the diagnosis may be made. Many cases are featured by asthma and eosinophilia and signs of glomerular nephritis. These findings were not present in the case being reported. It is with regret that nothing can be added to the therapy or the etiology of periarteritis nodosa. In the opinion of this reporter, the disease is more common than previously realized.

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COMPLETE A-V BLOCK IN A FETUS

CASE REPORT

CAPTAIN ROBERT K. PLANT, M.C., AND MAJOR ROBERT A. STEVEN, M.C.

A WOMAN, aged 26 years, gravida i, Register No. 12187, was seen in the prenatal clinic at Torney General Hospital, Palm Springs, California, on Feb. 14, 1944. Her last menstrual period occurred on June 12, 1943, making her expected date of confinement March 19, 1944. Her pregnancy had been uneventful except for slight spotting which had occurred at the time of the third and fifth missed menstrual periods. The general physical and laboratory findings were essentially negative. The fundus extended 6 fingerbreadths above the umbilicus with the fetus in the left occipito-anterior position. The maternal heart rate was noted as 88 per minute, while the fetal heart rate was noted as 60, regular, and not affected by pressure on the fundus. The patient was observed at approximately weekly intervals until term, and at each visit the fetal heart rate was found to vary between 50 and 60 per minute. It was regular and not affected by pressure on the fundus. A flat roentgen film of the abdomen on March 3, 1944, disclosed no gross abnormalities of the fetus.

A fetal electrocardiogram on March 10, 1944, showed the fetal rate to be 56 and the maternal rate to be 74 per minute. The deflections due to the fetal heart showed no variation from normal in the short strips obtained (Fig. 1).

The patient delivered on March 20, 1944, after a fifty-nine-hour labor. Prolonged labor was due to primary atony of the uterus. During labor it was noted that the fetal heart rate remained between 50 and 60 per minute and was not affected by labor pains. At birth, the child (Register No. 12242) was seen to be a well-developed male infant weighing 8 pounds 2¼ ounces and having a normal cry and respirations. The color was normal except for moderate cyanosis of the palms of the hands and the soles of the feet. This was not more severe than is often found in a newborn infant. An hour or two after birth the color of the nail beds was pink, and there was no cyanosis anywhere. The baby was not irritable or cross and breathing seemed easy and free. Examination of the infant's heart revealed the point of maximum intensity to be just medial to the mid-clavicular line, but pulsation could be felt in the epigastrium giving the impression that there was some cardiac enlargement. The rate was 52 per minute and the rhythm was regular with no variation with respirations. The heart sounds were normal. There was a soft, blowing systolic murmur in the left second intercostal space, near the sternum, which was not transmitted and which was interpreted as a physiologic murmur. X-ray examination of the heart showed gross cardiac enlargement. An electrocardiogram taken about three hours after birth (Fig. 2) showed complete A-V dissociation with a ventricular rate of 50 per minute and an auricular rate of 114 and marked right axis deviation.

The baby's weight dropped to 7 pounds 9 ounces on the third day of life and rose to 7 pounds 12 ounces about the sixth day of life. The baby did not nurse well. Pallor developed which gradually became more marked. On the morning of March 26, 1944, the infant developed definite cyanosis, and the liver was felt 2 fingerbreadths below the costal margin. Cyanosis rapidly became more marked, and at 2:00 P.M. the infant expired.

An electrocardiogram taken March 22, 1944, was identical with the first one except that the auricular rate had risen to 134 per minute, and a third tracing, taken on the day of death, showed an auricular rate of 150 per minute, with inversion of T₁ and T₄ (Fig. 3).

AUTOPSY REPORT

The autopsy was performed by Lieutenant Colonel Hans F. Smetana. Our brief extract from his report follows, giving only the pertinent findings but including in toto the microscopic examination of the heart:

The heart was grossly enlarged, weighing 56 grams (normal, 20.6 grams) and had flattened the lungs, especially on the left, posteriorly and laterally against the rib cage. The

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ductus arteriosus appeared closed. No septal defects were present and the valves were normal. The distribution of coronary vessels was normal. The pulmonary conus was quite large.

The lungs showed extensive atelectasis and early bilateral bronchopneumonia. There was passive hyperemia of the spleen, liver, kidneys, and brain. The liver extended 4 cm. below the costal margin. There was some hemorrhage into the meninges and a small hematoma in the galea aponeurotica in the occipital region, presumably due to forceps.

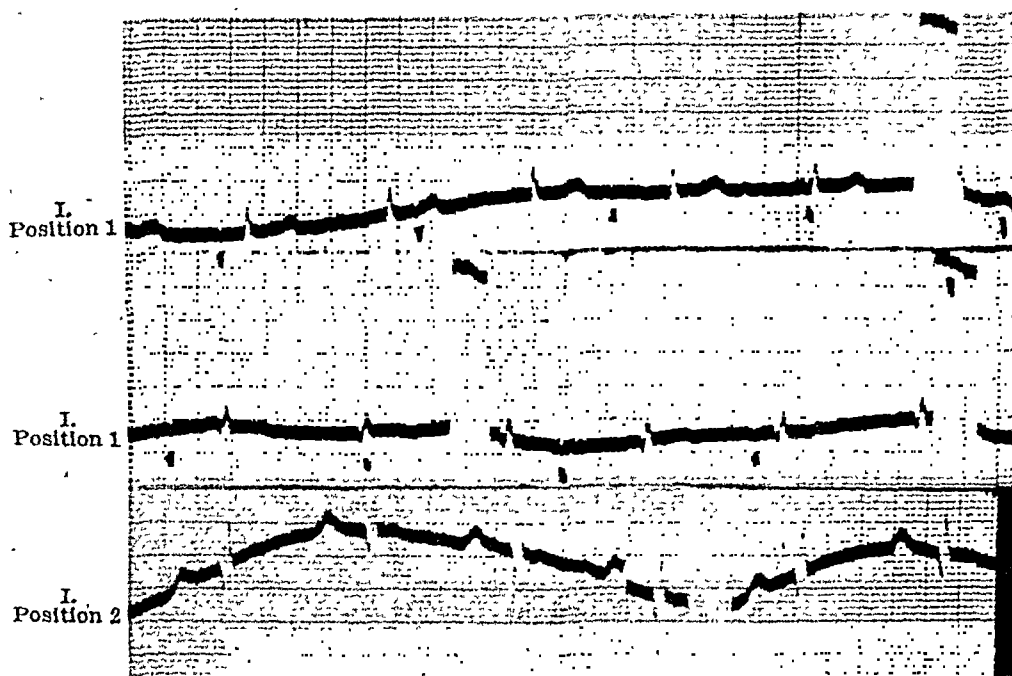


Fig. 1.—Electrocardiogram taken March 10, 1944.

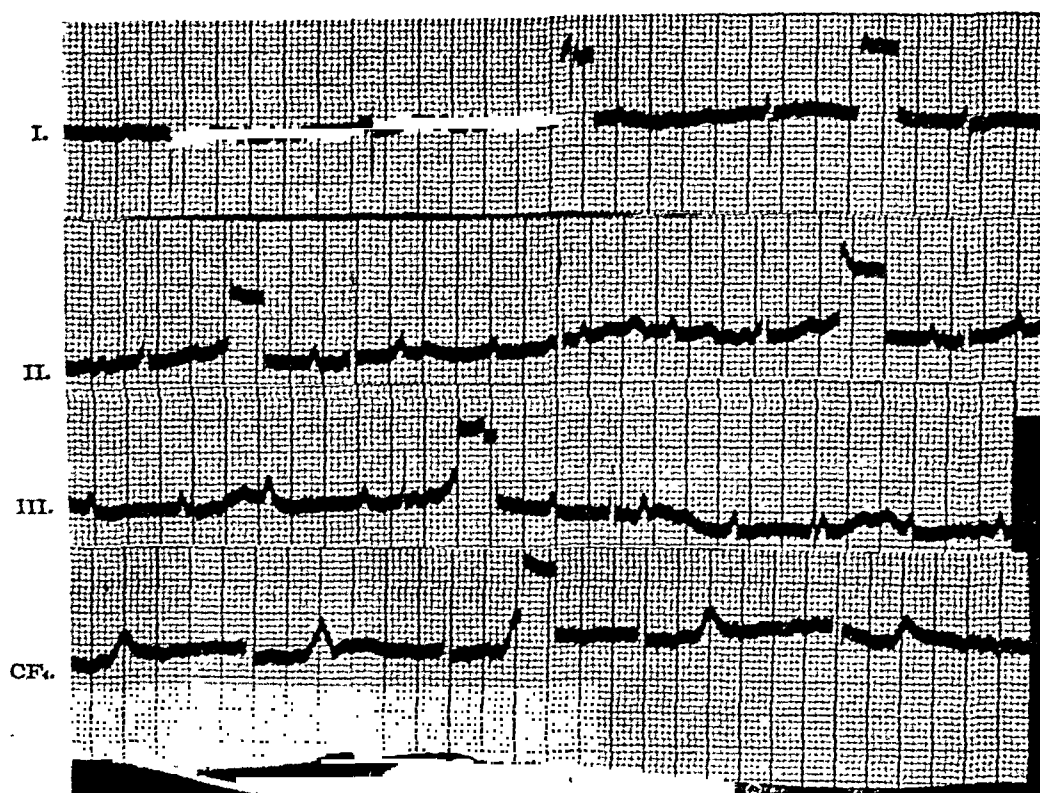


Fig. 2.—Electrocardiogram taken March 20, 1944.

Heart.—Section A: This is a cross section through the interventricular septum just beneath the membranous septum and includes parts of the walls of the right and left ventricles. The endocardium of the septum facing the right ventricle is of normal thickness

and shows no Purkinje fibers of the bundle of His. The myocardial fibers of the septum and of the wall of the ventricle are of normal size. Their cross striations can just be made out. The endocardium facing the left ventricle is thicker than that on the right and the borderline between it and the myocardium is somewhat irregular. Halfway between the endocardial surface and the myocardium are a few strands of muscle fibers with abundant fibrillae showing cross striations which are as definite as those of the fibers of the myocardium. These strands, however, are separated from the main myocardium by rather dense collagenous fibrous tissue. There is moderate congestion of the capillaries of the myocardium especially in the left superficial layers of the septum and minute hemorrhages seem to have occurred. There is no inflammatory reaction. The epicardium is not remarkable. The vessels in the subepicardial fat tissue appear normal. *Phosphotungstic acid stain*: The subendocardial muscle fibers show a normal fibrillar arrangement with cross striations. Some of these fibers appear vacuolated. The fibrillar structure of the myocardial fibers appears normal.

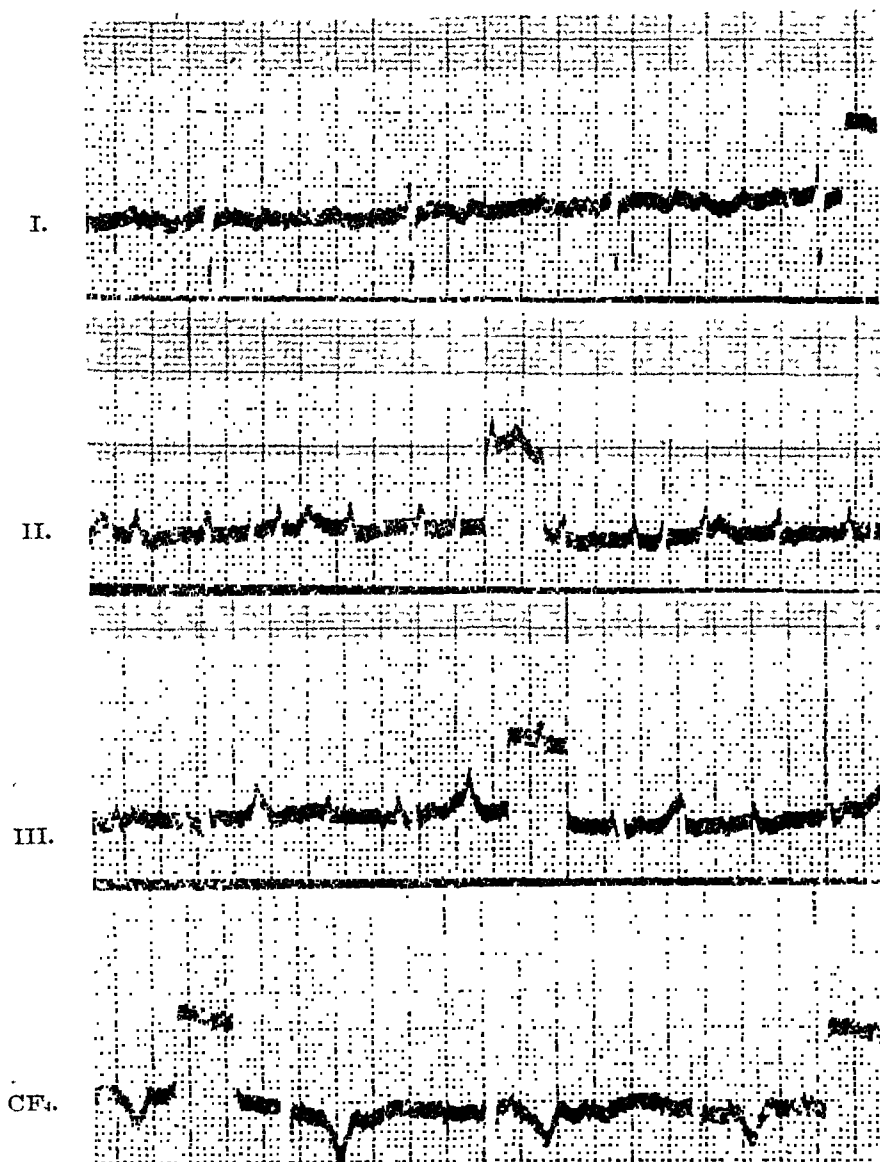


Fig. 3.—Electrocardiogram taken March 26, 1944.

Section B: This is a section through the prominence on the anterior surface of the heart and includes the interventricular septum. No Purkinje fibers are recognized in the endocardium on either side of the septum. A few groups of muscle fibers beneath the endocardium facing the left ventricle are separated from the main myocardium by a fibrous band but the character of the fibers is not that usually encountered in the bundle of His. There is no inflammatory reaction. The peculiar and complicated character of the pulmonary conus is well brought out in this section. The myocardium appears normal. The epicardium is normal. *Phosphotungstic acid stain*: There is no significant difference in the structure of the myocardial fibers beneath the endocardium from those of the main myocardium. *Best's carmine stain*: No glycogen-containing fibers are seen beneath the endocardium of the interventricular septum on either side nor within the main myocardium.

Aorta.—The aorta is normal.

AUTOPSY SUMMARY

At autopsy the most outstanding finding was a very large heart causing compression of both lungs with partial atelectasis. No gross structural defects were noted in the heart and there were no congenital malformations except a large pulmonary conus. In order to be able to demonstrate possible changes of the bundle of His the entire heart was fixed in formalin saturated with dextrose to preserve the glycogen of the Purkinje fibers. Frozen sections as well as paraffin sections, taken from the septum of the ventricles, failed to show subendocardial fibers which can be identified as Purkinje fibers. Since there is no septal defect, the complete heart block is tentatively attributed either to absence or faulty development of the bundle of His. The enlargement of the heart is considered to be secondary to the slow heart rate resulting in anoxemia.

Death is attributed to the circulatory failure and partial atelectasis of the lungs complicated by early bronchopneumonia. The birth trauma of the brain, as demonstrated by the meningeal hemorrhages and cellular infiltrations over the left occipital lobe, is perhaps a contributory factor.

COMMENT

No discussion of fetal electrocardiography is intended or necessary here. There is a fairly extensive literature on this subject. Suffice it to comment that to date the only information to be gained from a fetal tracing is determination of the cardiac rate or, in the case of multiple pregnancies, rates. This has been made practical largely through the use of amplifiers. The authors were using the Sanborn cardiette but were able to get only an amplification of 2.5 times instead of the anticipated 6 times; as a result the deflections were quite small but nevertheless clearly discernible. Lead I wires were used. Electrodes were placed in the epigastrium and the right lower quadrant for Position 1. Several other positions were used but no deflections obtained.

From the examinations of frozen and paraffin sections noted, it appeared that the cause of the block was an absence or imperfect development of the bundle of His. Further studies were carried out by the Army Medical Museum. The letter from the Museum, signed by Lieutenant Colonel Balduin Lucke, Deputy Curator to the Chief of Laboratory Service, Torney General Hospital, follows:

"1. We are in agreement with your findings in the interesting case of G.D.G., your #51, A.M.M. Acc. 109014. Additional blocks were cut from the material submitted, and we have been unable to identify with any certainty the fibers of the conduction system. We believe that the heart block consequently must be related to the maldevelopment of the conduction system."

To the authors' knowledge, complete heart block has not been recognized in utero before. The slow rate plus the failure of the rate to vary with uterine contractions led us to feel that we were dealing with complete A-V dissociation.

ANNULUS FIBROSUS CALCIFICATION OF THE MITRAL VALVE

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RICHMOND, VA.

CALCIUM deposition in diseased heart valves may be demonstrated frequently in necropsy studies, but these deposits are usually overlooked clinically unless the heart is carefully examined roentgenographically. Sosman¹ discusses in detail a simple method of demonstrating the presence of calcific deposits within the heart by x-ray. He suggests a small fluoroscopic aperture and a screen of high intensity, using a 5-inch gap and 5 ma., to locate the calcified valves. The patient is rotated into a slight anterior right oblique position, about 15 to 20 degrees; then the examiner looks through the heart along the line of the auriculoventricular sulcus. This region can be identified by finding the auriculoventricular junction on the left border and searching obliquely across the heart shadow downward and medially, 45 degrees from the horizontal from this point. In this position, both the aortic and mitral valve calcifications are best seen, but they are difficult to differentiate. If intracardiac calcification is found, the patient is rotated to the left anterior oblique position. In this position, the mitral valve is in the posterior third of the heart shadow, while the aortic valve is in the mid-third. The valves will show up as dense irregular nodular masses, similar in appearance to calcified mesenteric glands, and they are darker shadows within the dark heart shadow. Rings of fibroelastic tissue at the roots of the cardiac valves, known as the annuli fibrosi, may become calcified and appear as a solid mass, having a J-shaped or U-shaped appearance. This is usually considered a senile change, associated with other evidence of senility, such as Mönckeberg's sclerosis, arcus senilis, and calcified intervertebral discs. It is associated very seldom with organic heart disease. This particular case is presented because of the finding within the heart of a large calcified mass, apparently not associated with any demonstrable evidence of organic cardiac disease.

CASE REPORT

History.—A white man, aged 38 years, complained of indigestion for several years. In April, 1944, he was referred to Dr. Fred Hodges for a gastrointestinal x-ray study. This proved to be negative, but during the investigation a deposit of calcium was demonstrated within the heart. The patient had never complained of any cardiorespiratory difficulty, but during a superficial examination in 1939, was told that he had a heart murmur. His childhood had been uneventful except for frequent sore throat. There was no history of rheumatic fever or any other unusual ailments.

Physical Examination.—The patient was tall and spare, weighing 116 pounds and appearing much older than his stated age. There was a right divergent squint and opacities were evident in both optic lenses. There was moderate arteriosclerosis of the retinal vessels without hemorrhages or exudates. The patient had a marked kyphosis of the spine, involving the upper thoracic vertebrae. The lungs were clear. The blood pressure was 130/85 in both arms. The heart was not enlarged. There was a short systolic murmur, heard best at the apex and transmitted to the left axilla. There was no thrill. The pulmonic second sound was slightly accentuated. The aortic sounds were normal. The abdomen was soft and no masses were palpated. The radial arteries were moderately thickened. The extremities and reflexes were negative.

From the Department of Cardiology, Medical College of Virginia.
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Laboratory Studies.—The blood Wassermann test was negative. There was no sugar or albumin in the urine. The red blood count was 4,300,000 per cubic millimeter; the hemoglobin was 85 per cent (Sahli). An electrocardiogram was considered within normal limits, and a stethogram demonstrated a moderately intense systolic murmur at the apex.

Fluoroscopy.—The lungs were clear; the heart was small and in the mid-position. The right border was straight. The pulmonic conus was not enlarged. A large calcified mass was visible within the heart in all positions. This mass was situated along the margin of the left ventricle in the region of the mitral valve. In the left oblique position the mass was more prominent, lying posteriorly in a semilunar curve, 7 cm. in length and about 6 mm. in diameter. The mass moved within the heart at each pulsation.

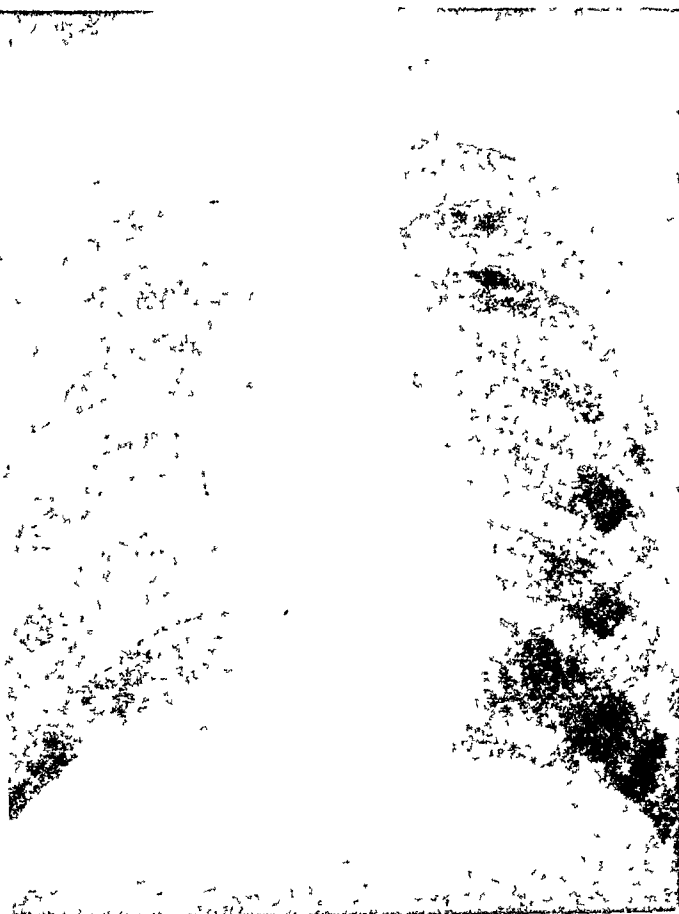


Fig. 1.



Fig. 2.

Fig. 1.—Calcification of mitral annulus fibrosus. Roentgenogram of chest, posteroanterior position. A small heart with straight right borders. Calcified mass within the left ventricle.

Fig. 2.—Calcification of mitral annulus fibrosus. Roentgenogram of chest, left lateral position; calcified semilunar mass in posterior third of the heart shadow.

DISCUSSION

Intracardiac calcification is not rare. There have been many studies concerning calcification within the heart, caused by arteriosclerosis or by superimposed deposits of calcium on rheumatic valves. It has been emphasized that deposition of calcium on the valves is characteristic of rheumatic heart disease.² It would seem wise to make a distinction between calcified valves and calcification of the annulus fibrosus. This is a rather difficult problem, as the annuli fibrosi lie at the bases of the valves, but Sosman¹ has shown that, when a valve becomes calcified, it appears as a group of small, irregular, nodular masses, but the annulus fibrosus calcification is a solid mass having a curved appearance. It is believed that in our case there is a calcified annulus fibrosus. The patient had generalized arteriosclerosis and bilateral cataracts and looked to be about 60 years of age, although he was only 38. There was nothing in the history suggestive of old rheumatic heart disease. The murmur at the apex was not con-

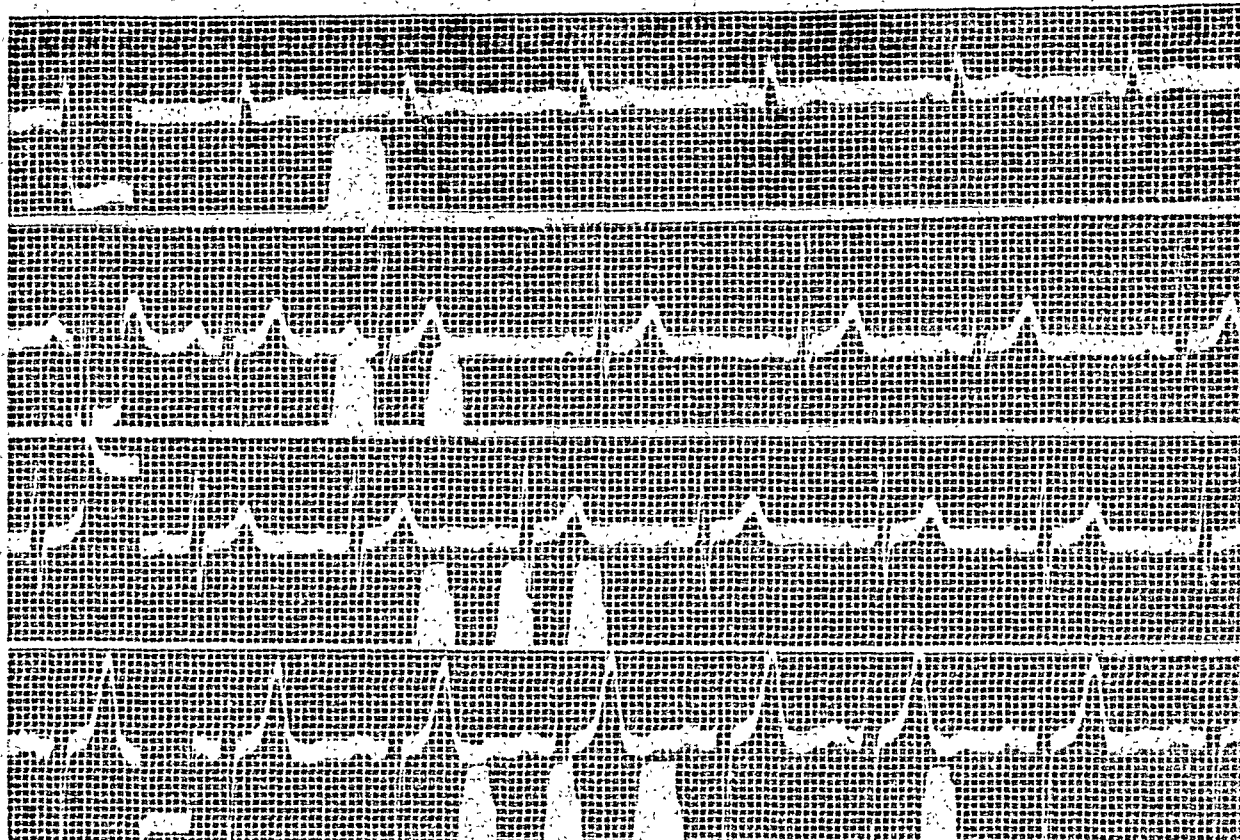


Fig. 3.—Calcification of mitral annulus fibrous. Electrocardiogram; the tracing was considered within normal limits.

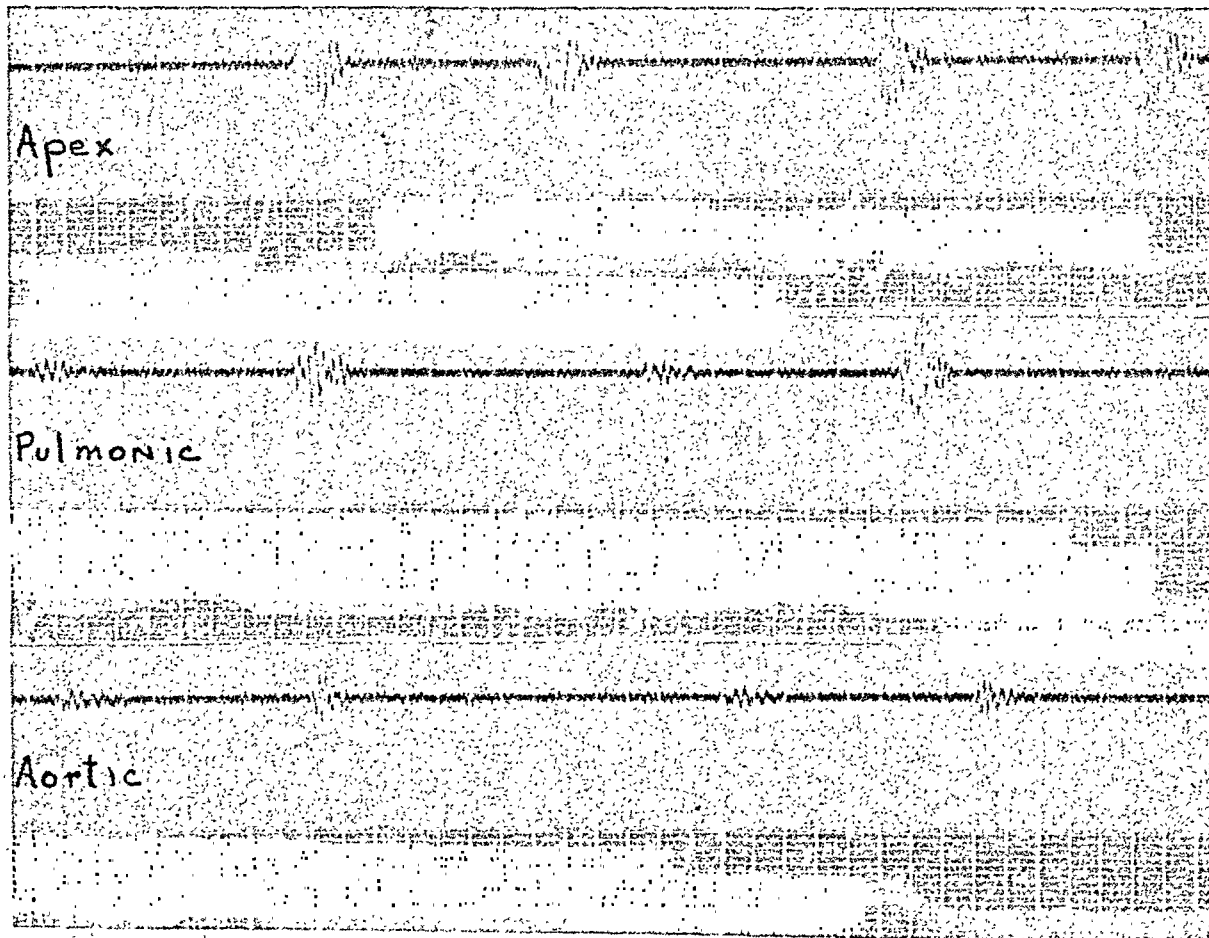


Fig. 4.—Calcification of mitral annulus fibrous. Stethogram; the increased vibrations at the apex are considered as due to a soft systolic murmur.

clusive, and the heart itself did not have the contours usually seen in mitral valve disease. The intracardiac calcification in this man was probably a degenerative change due to premature senility.

CONCLUSION

Calcification within the heart may be demonstrated frequently by the fluoroscope. Knowledge of the type of calcification and the area involved aids considerably in the clinical diagnosis. This case is presented as one of calcification in the annulus fibrosus of the mitral valve.

We wish to thank Drs. T. N. Barnett and Fred M. Hodges for allowing us to report this case.

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CONTUSION OF THE HEART

A CASE REPORT

MAJOR LEWIS K. REED, M.C., AND CAPTAIN KNUTE E. BERGER, M.C.

THE following case of cardiac trauma due to a blow on the chest is of interest because it is possible to estimate the force producing the injury and to follow the electrocardiographic changes from shortly after the accident until complete recovery.

CASE REPORT

Present Illness.—The patient was a white aircraft mechanic, aged 26 years. At 4:30 P.M. on Dec. 11, 1943, he was helping four other men attach the trailer arm of a fully loaded, 2,000 gallon gasoline trailer to a tug. In lifting the arm above the horizontal to attach it to the pintle hook of the tug, the forward dolly to which the trailer arm was attached suddenly rotated, and the arm snapped upward, pinning the patient between the trailer arm and the bottom of the gas tank (Fig. 1). The patient cried out, became red in the face, and lapsed into unconsciousness. It required the concerted efforts of five men pulling down on the end of the trailer arm to lower it and release the patient. He was impinged for somewhat less than one minute and remained unconscious for about one and one-half minutes after release.* On admission to the hospital thirty minutes after the accident, the patient complained of weakness and steady precordial pain which did not radiate to the neck or arms.

Physical Examination.—The patient was a slender white man, 69 inches in height and 178 pounds in weight. On admission he was pale and moderately dyspneic but not cyanotic. His neck veins showed no distention, the trachea was in the midline. *Lungs:* The expansion was equal; there was no abnormality of percussion or auscultation. The respiratory rate was 30 per minute. *Heart:* No visible or palpable increase of precordial activity could be observed. The cardiac apex was 7.5 cm. to the left of the midsternal line in the sixth intercostal space. The right border was at the right sternal margin. The heart sounds were well heard and there were no murmurs audible. The rhythm was completely irregular. The apical

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*From weight and measurement data obtained on the trailer, calculations were made by a mechanical engineer indicating that the trailer arm, in its sudden upward swing, delivered an estimated force of approximately 2,000 pounds. This force was expended on the patient's chest, protected by a fleece-lined, leather flying jacket over the usual fatigue uniform and undershirt.

rate was 128 and the radial pulse was 88 per minute. The blood pressure was 110/60. *Abdomen:* Negative.

The clinical impression on admission was cardiac contusion with auricular fibrillation. The patient was given $\frac{1}{4}$ grain of morphine sulfate and placed on strict bed rest. The first electrocardiogram (Fig. 2) was taken about two hours after the injury. Roentgenograms of the chest the morning following the injury showed an apical pneumothorax representing about 3 per cent collapse of the right lung; the cardiac silhouette was normal; a flat roentgenographic film of the abdomen was negative.

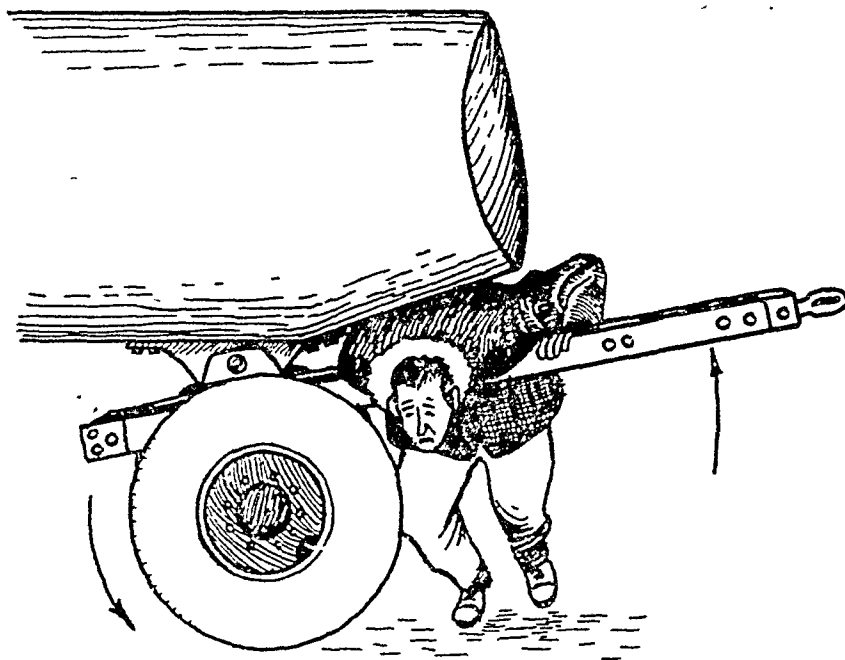


Fig. 1.—Illustration of manner in which the soldier was pinned between 2,000-gallon gasoline trailer and connector-tongue to tractor.

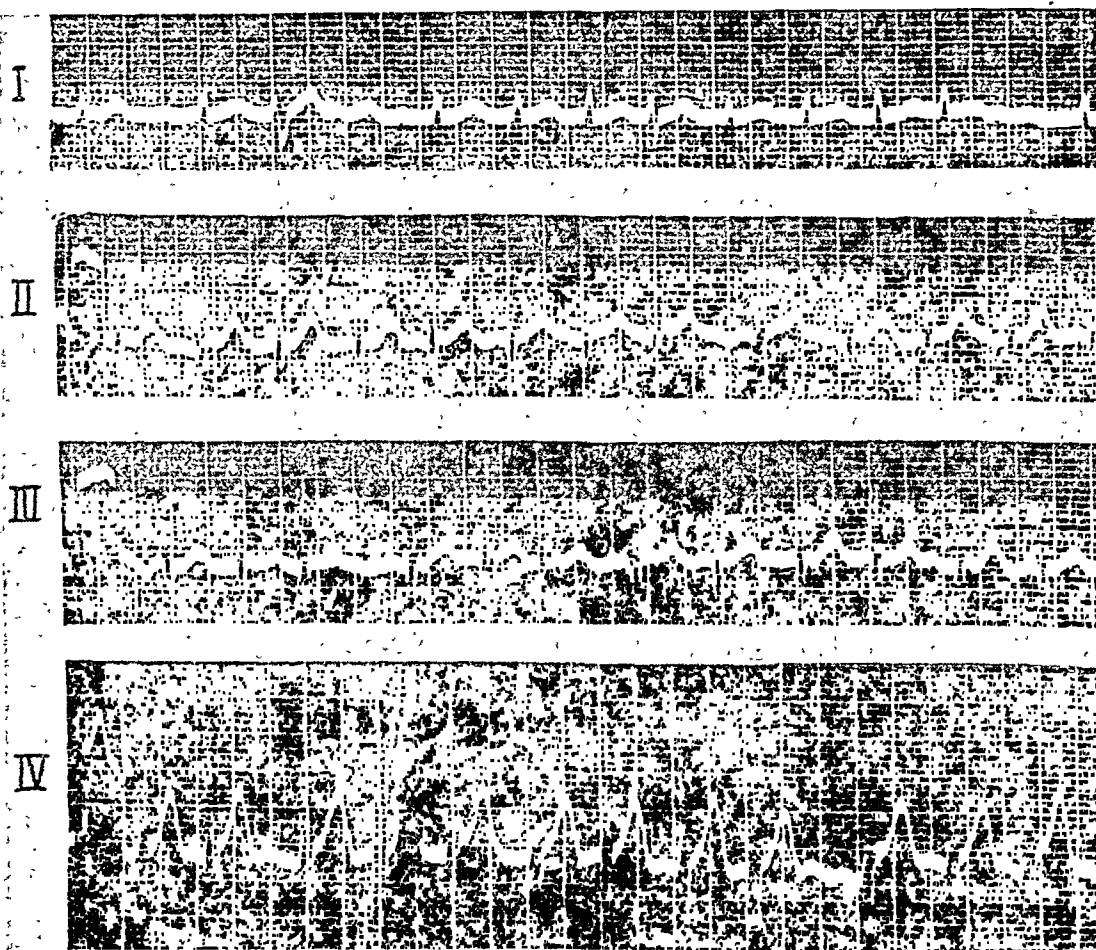


Fig. 2.—Electrocardiogram taken about four hours after injury. The variation in size of ventricular complexes indicates that auricular fibrillation is just ceasing or about to begin. There is an occasional ventricular premature beat, probably arising in the left ventricle (Lead I).

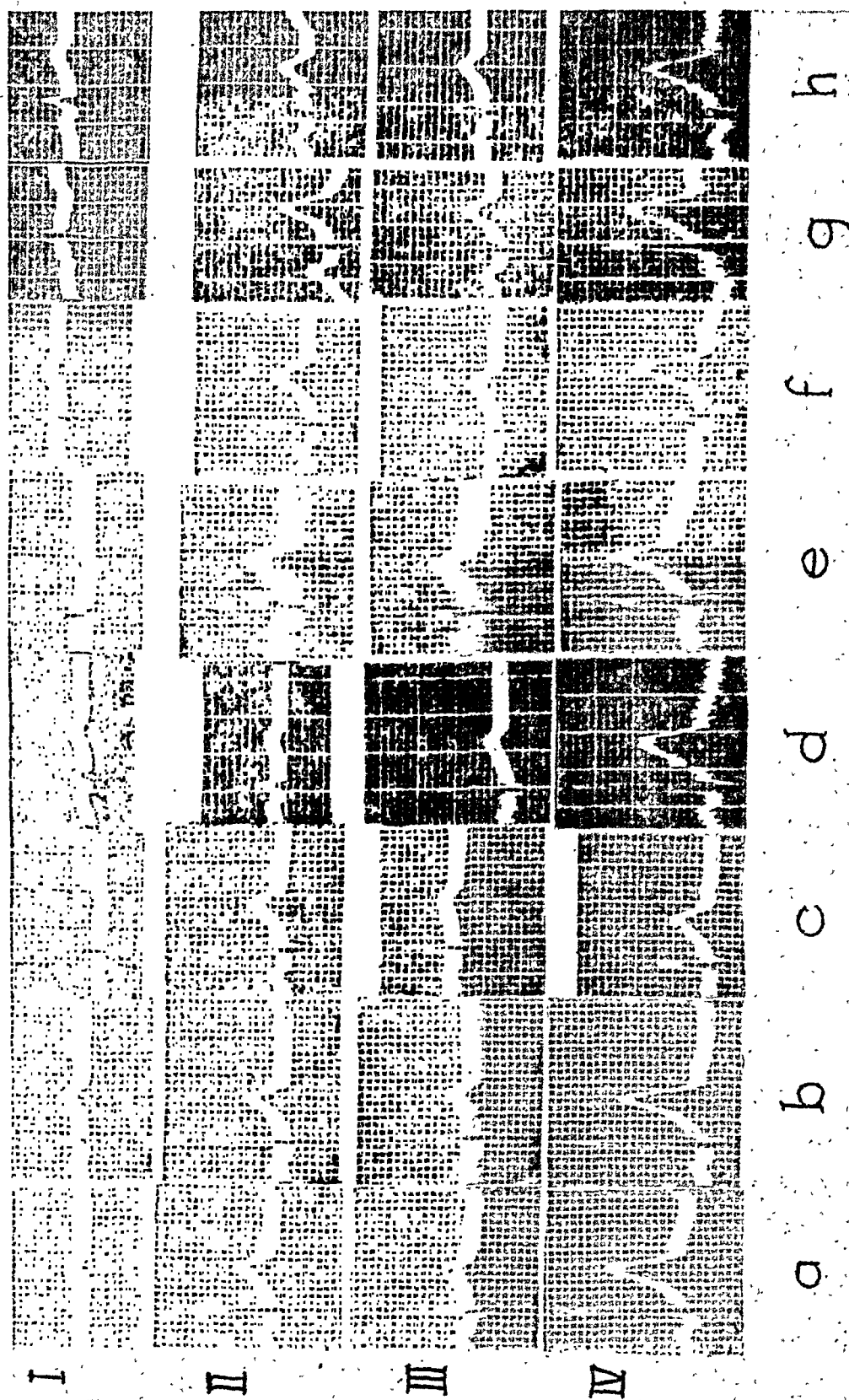


Fig. 3.—Serial electrocardiograms: *a* and *b* taken on Dec. 12 and 14, 1943, respectively, show no abnormality; *c*, Dec. 22, 1943, patient wheeled in chair to electrocardiographic laboratory and transferred to table. Electrocardiogram shows evidence of slight right axis deviation and mild right ventricular strain, acute; *d*, Dec. 24, 1943, patient in bed. Electrocardiogram shows slurring QRS in Lead II, manifesting some myocardial damage; *e*, Dec. 31, 1943, patient returned to electrocardiographic laboratory by wheel chair, again the electrocardiogram shows some evidence of mild right strain; *f*, Jan. 8, 1944, patient in wheel chair, electrocardiogram normal; *g*, Feb. 4, 1944, patient ambulatory convalescent, again the electrocardiogram shows slight evidence of strain, no symptoms; *h*, Feb. 9, 1944, patient ambulatory, electrocardiogram normal. All subsequent records were normal.

Past History.—The patient had always been healthy, having had the usual mild, childhood diseases. He denied rheumatic fever, scarlet fever, renal or venereal disease and had always had good exercise tolerance with no cardiorespiratory symptoms. On the day preceding the accident he had undergone a complete, routine physical examination to determine his fitness for overseas duty. The pertinent findings at that time were: "Heart, normal; blood pressure, 130/84; pulse, sitting, 80; pulse, immediately after exercise, 100; character of pulse, normal; arteries, normal; blood Kahn test, negative; urinalysis, normal."

Hospital Course.—Clinical evidence of arrhythmia ceased about seven and one-half hours after admission. Serial electrocardiograms are shown in Fig. 3, the first of which (a) was taken about 9 A.M. the morning following the accident. On that day he had mild substernal pain, without exertion, and some difficulty in swallowing solid food. The heart sounds were well heard, the rhythm was regular, and the pulse was 90 with no deficit. During the first two days following the injury his temperature ranged from 99° to 99.6° F. after which time he remained afebrile during the entire convalescence. On the third day he developed some soreness on swallowing which he localized to the insertion of the right sternocleidomastoid muscle. Examination of the chest revealed a friction rub on deep inspiration along the upper portion of the right sternal border. This had disappeared on the following day, but he continued to have a pleuritic pain in the right side of the chest anteriorly. By the sixth hospital day he was clinically well. X-ray films at this time showed that the pneumothorax had disappeared. Throughout the convalescence the blood pressure ranged from 100 to 116, systolic, and 60 to 70, diastolic. There was never a significant difference in blood pressure between the two arms. On the day following admission the leucocyte count was 10,150 per cubic millimeter, with 62 per cent neutrophils. Frequent counts thereafter revealed a rapid return to normal. Sedimentation rates done on the third, seventh, and nineteenth hospital days were 48, 38, and 10 mm. per hour, respectively. All urine specimens were normal.

The patient was kept in bed for four weeks. Despite orders, he got out of bed on the fourteenth and sixteenth hospital days. At these times he developed moderate palpitation but no pain or dyspnea. On the seventeenth hospital day he volunteered symptoms suggesting extrasystoles, and clinical examination proved the presence of this condition. It will be noted in Fig. 3 that in each instance when the patient was moved in a wheelchair to the electrocardiographic laboratory the record shows evidence of a mild degree of strain.

Following four weeks of bed rest the patient was up progressively with restriction of activity and was given a graded convalescent program with increasing exercise for a period of five weeks. During this period he occasionally complained of brief periods when his heart "seemed to skip a beat"; these were apparently not related to physical activity. During the latter five weeks, in the hospital no examiner was able to find any irregularity at the times of examination.

Re-examinations at three and four months after the injury were completed and were entirely negative. The patient was able to do full duty without complaint.

COMMENT

Kahn and Kahn¹ pointed out, in 1929, that the position of the heart directly behind the sternum and adjacent cartilages exposes it to injury from non-penetrating trauma to the adjacent chest wall. They showed that cardiac arrhythmias, heart block, and even rupture of heart valves could occur in the absence of external injury to the chest. Bilderbeck² reported a rupture of the right auricle immediately due to a blow on the chest without any evidence of injury to the thorax. Bright and Beck³ showed that patients with cardiac contusion may die of cardiac rupture, especially during the second week after injury when myomalacia exists. Beck⁴ pointed out that cardiac rupture is a rare complication of cardiac contusion and that the heart muscle can tolerate an excessive amount of trauma as demonstrated in dog experiments. Moritz and Atkins⁵ traumatized dog hearts and demonstrated, following contusion, single or multiple areas of focal hemorrhagic necrosis in the myocardium either at, or remote from, the site of trauma. This focal necrosis gives way to the formation of myocardial scars. Beck pointed out that, in the absence

of rupture, cases of cardiac contusion in general should be treated in the same manner as coronary thrombosis.

Many cases of direct and indirect cardiac trauma have been reported in the literature, but the protocols universally lack data as to the exact force applied and usually are wanting of electrocardiographic tracings taken immediately after the trauma, and complete histories and physical examinations prior to the injury are not given. In the case herein described the established 2,000 pounds' striking force applied to the patient's chest may seem disproportionate to the injury received. Undoubtedly a portion of this force was dissipated by the heavy fleece-lined jacket which he was wearing. Furthermore the force was distributed over the entire flat surface of the chest anteriorly and posteriorly. The resiliency of the chest wall in a person of this age further tends to dissipate the force of such an injury as was herein described.

CONCLUSION

1. This case study confirms the work of other authors in proving, beyond doubt, that the heart may be injured by external trauma without evidence of injury to the chest wall.

2. This case demonstrates that a force which would ordinarily be considered lethal when applied directly to the chest, can be survived.

3. This study confirms the accepted treatment of cardiac contusion, namely the treatment of coronary occlusion.

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Abstracts and Reviews

Selected Abstracts

Hoffmann, F., Hoffmann, E. J., Middleton, S., and Talesnik, J.: The Stimulating Effect of Acetylcholine on the Mammalian Heart and the Liberation of an Epinephrine-like Substance by the Isolated Heart. *Am. J. Physiol.* 144: 189, 1945.

The injection of acetylcholine into the isolated atropinized hearts of dogs, cats, rabbits, and guinea pigs regularly causes an epinephrine-like effect, i.e., an increase of heart rate and amplitude, as well as a change of blood flow in the coronary vessels.

The positive ino- and chronotropic effects of acetylcholine are abolished by ergotamine, by curare, and by nicotine.

The pharmacological characteristics of the stimulating action of acetylcholine on the heart enables us to designate it as "nicotine-like."

In the perfusate of the isolated heart, it is possible to identify the presence of an epinephrine-like substance liberated when acetylcholine or nicotine is injected into the heart. Under the stimulus of these drugs the perfusate acquires an activity which can be demonstrated by its positive inotropic action on the hypodynamic frog heart and by a relaxing effect on the rectal cecum of the fowl and on the small intestine of the rabbit.

AUTHORS.

Lawson, H., and Rehm, W. S.: The Effect of Hemorrhage and Replacement on the Apparent Volume of Plasma and Cells. *Am. J. Physiol.* 144: 199, 1945.

No evidence was obtained for an increase in the rate of disappearance of the dye T-1824 during almost complete exsanguination or in the four-hour period following reinjection of blood, in experiments on barbitalized dogs. Indirect measurement of circulating plasma volume during exsanguination therefore seems legitimate. Such measurements indicated that fluid was added to plasma at the mean rate of 0.154 ± 0.0114 c.c. per kilogram per minute when blood was drawn at the rate of 2 c.c. per kilogram per minute until mean arterial pressure fell below 20 mm. of mercury. When the animals were kept alive by reinjection of blood and were bled to death at the same rate four hours later, the rate of plasma replenishment during the second bleeding was only 0.088 ± 0.0119 c.c. per kilogram per minute. The rate of addition of fluid to plasma was usually increased at the time when arterial pressure began to decline steeply during the bleeding.

Evidence was obtained that the circulating cell volume is overestimated by an average of about 29 per cent if it is calculated from the plasma volume and the hematocrit in drawn blood. When measured by this method, the gain in circulating cells following injection was about 29 per cent greater than the volume injected; and the loss during bleeding was about 29 per cent greater than the volume withdrawn. The percentage error seems to remain fairly constant throughout all stages of exsanguination. The error appears in most cases to be completely masked during the first bleeding in our experiments, presumably by expulsion of cells from the cell reservoirs.

AUTHORS.

Black, W. A., and Karpovich, P. V.: Effect of Exercise Upon the Erythrocyte Sedimentation Rate, *Am. J. Physiol.* 144: 224, 1945.

1. Fifty aviation cadets, convalescing from upper respiratory infection, were given five minutes of strenuous exercise (the Harvard step-up test).

2. Blood samples were taken immediately before exercise, and half an hour, five hours, and twenty-four hours after exercise. The erythrocyte sedimentation rate was determined by the Westergren method.

3. Five minutes of strenuous exercise caused a variable effect upon the individual sedimentation rate. However, in the group tested there was a statistically significant increase

in erythrocyte sedimentation rates five hours after exercise but no significant change either half an hour or twenty-four hours after exercise. This indicates that the change is not lasting.

4. Post-exercise observations in no case showed any clinical manifestations of ill effects.

5. Data on thirty-nine subjects showed that there was no relation between the erythrocyte sedimentation rate before exercise and the score obtained on the Harvard step-up test ($r = -0.15$).

6. The contradictions regarding the effect of exercise upon the erythrocyte sedimentation rate found in the literature may be explained by the difference in the intensity of exercises and in the time of taking the blood samples. AUTHORS.

Lepera, L., and Pataro, F. A.: Normal Mean Zone of Values of the Precordial QRS in Normal Subjects, *Rev. argent. de cardiología* 12: 26, 1945.

In 100 normal persons a study was made of the mean value and the standard deviation of the QRS duration and of the voltage of its waves in precordial leads CF_1 to CF_6 , arriving at the following conclusions:

The greatest mean value of QRS duration was 0.088 seconds in lead CF_2 , the normal range being from 0.078 to 0.098 seconds.

The greatest mean value of Q resulted in CF_2 (1.3 mm.), the normal range being from 0.1 to 2.5 millimeters.

It was also in lead CF_2 where the greatest mean value of R voltage (12 mm.) was observed with normal limits between 6 and 18 millimeters.

Concerning the deepness of S its greatest mean value was observed in CF_2 (20.9 mm.), the normal values ranging from 15.8 to 26 millimeters.

In all cases the normal values were calculated on the basis of the mean value and the standard deviation. The wide variations of the latter are discussed. AUTHORS.

Schill, E.: Sinus Extrasystole With Consecutive Disturbance of Conduction in the Total Conduction System, *Cardiologia* 6: 271, 1942.

Description and analysis of a case in which, in consequence of sinus extra systoles, a disturbance of the stimulus conduction between sinus and auricle as also between auricle and ventricle, corresponding the Wenckebach period, was observed. The deviation of the atrio-ventricular conduction periods from the known Wenckebach periods is caused by the extra auricle waves, which occur in ever shorter periods, a condition which is to be explained by the oft repeated demands and consequent deterioration of conduction between sinus and auricle in the sense of the Wenckebach periods. In other words, the functional disturbance of two functionally and spatially coordinated parts of the stimulus conduction system does not reveal itself spontaneously and independently, whereby the disturbance of the upper situated part of the phenomena influences the functional disturbances of the lower situated part. In consequence of the increased number of extra systoles in a short time and the consequent greater demands, the intraventricular condition was also disturbed. Fundamental for the phenomena described is the not intact, only by low frequency normally functioning stimulus conduction system. The cause of the trouble in the stimulus conduction system is unknown, most probable in sclerosis of the corresponding artery. AUTHOR.

Saphir, O.: Laryngeal Edema, Myocarditis and Unexpected Death, *Am. J. M. Sc.* 210: 296, 1945.

Five children who rapidly developed symptoms of upper respiratory obstruction and succumbed quickly, despite tracheotomy, are recorded. Autopsies disclosed severe laryngeal edema, edema of the epiglottis and subglottic area, and acute myocarditis. The edema is interpreted as an early stage of so-called laryngotracheobronchitis. The unexpected death was probably caused by myocarditis. If the attending physician in future instances is aware of this complication, supportive measures might forestall the fatal outcome. AUTHOR.

Moguel, E. B.: Histologic Structure of the Valvular Endocardium, *Arch. Inst. cardiología México* 15: 113, 1945.

A study of the cardiac valves in the normal adult was undertaken, in which aniline techniques were used to stain the elastic fibers and argentic impregnation of the precollagen structure; this resulted in the discovery of the following unpublished data.

All cardiac valves, beneath the endothelium, have a layer of extremely thin, rectilinear filaments of precollagen, slightly or not at all ramified, usually running in a single direction

that form something similar to a basal membrane that offers support to thick elastic nets.

The spongiosa contains flexuous filaments that have a tendency to form ringlets and are slightly acidophilous; they must be considered as formed by a substance with characteristics intermediate between precollagen and collagen. This spongiosa, in all appearances, constitutes the most active component of the cardiac valves.

The fibrosa constitutes the skeleton of the valvular membranes and is made up in its entirety of very thick and rigid fascies of collagen.

The basal membrane reaches a greater development in the auriculoventricular valves than in the sigmoids and is reinforced by filaments of considerable thickness that lie athwart them. The subendothelium also has a reinforcement consisting of rigid strands of precollagen intermingled with elastic nets.

The spongiosa of the atrioventricular valves is polymorphous: near the base of implantation it has features which resemble those of the basal membrane, whereas toward the center the precollagenous filaments present soft undulations and tend to run in a single direction so as to reach the free edge in the form of long regularly flexuous and very lax curls; furthermore, the spongiosa of the auriculoventricular valves contains many anastomosed cells with a polyblastic capacity.

The fibrosa of the atrioventricular valves differs from that of the sigmoids due to its heterogeneous nature. At the base of implantation the fascies of collagen are dense and run in a single direction, whereas around the free edge the bundles intercross, frequently dissociating, all of which forms lax spaces in the zones comprised among the tendinous insertions.

No great variations are specified in the filamentous structure of the cardiac valves because those encountered do not present sufficient regularity and one has the impression that many of them may be pathologic.

All the fine argentophile fibers, especially the flexuous and slightly acidophilic ones of the spongiosa, are susceptible of transformation during inflammatory processes into thick, retractile, collagenous bundles. They are responsible for the main deformities found in abnormal valves.

Some of the elastic fibers of the cardiac valves, notably the finer ones, may under certain circumstances, take a silver stain; it is possible that such argentophilia may denote a morphogenetic relationship between these elastic fibers and the precollagenous structure.

AUTHOR.

Berconsky, I., and Cossio, P.: Pain in Epistenocardia Pericarditis, *Rev. argent. de cardiol.* 12: 1, 1945.

Based in clinical experience the authors claim that the epistenocardial pericarditis (post-infarction pericarditis) may account for the painful episode (acute or dull pain) which occurs sometimes one or two days after myocardial infarct.

This painful episode has its own qualitative and occasional peculiarities; for instance, its exacerbation by a deep inspiration, a circumstance which allows the prediction of friction rubs and eliminates the possibility of new infarctions. The authors recommend its control with amidopyrine or acetylsalicylic acid rather than morphine, unless the pain becomes intolerable. The characteristics of the pain and its diagnostic and therapeutical importance are made objective by a short account of three personal observations.

AUTHORS.

Watson, R. F., Rothbard, S., and Swift, H. F.: The Relationship of Postscarlatinal Arthritis and Carditis to Rheumatic Fever, *J. A. M. A.* 128: 1145, 1945.

The purulent complications and nonpurulent sequelae which occurred among 110 cases of scarlet fever in young adults who were intensively studied were analyzed. Group A streptococci, representing at least thirteen different types, were recovered on culture of the nasopharynges of 109 patients and a group C strain from the remaining one. Antistreptolysin O and antifibrinolysin titrations were made with the serums and plasmas, respectively, for all patients at weekly intervals.

Sixty-three patients had uncomplicated infections and made uneventful recoveries; twenty-nine suffered purulent complications; and twenty-two, including four who also had purulent complications, developed pronounced and unequivocal electrocardiographic abnormalities comparable with those seen in patients with active rheumatic carditis. Three of these twenty-two patients developed abnormal electrocardiograms during their acute streptococcal infection and the other nineteen during postscarlatinal convalescence. It is this latter group of nineteen patients who are of particular interest in this study.

Eight of the nineteen patients who developed electrocardiographic abnormalities during postscarlatinal convalescence had definite clinical attacks of rheumatic fever of varying severity. Four others differed from these eight in that their rheumatic-like manifestations were milder and more transitory. The remaining seven during a comparable period in their convalescence developed similar electrocardiographic abnormalities without other symptoms of rheumatic fever, although several had brief secondary rises in temperature, leucocyte count or erythrocyte sedimentation rate. The difference between these three groups of patients is quantitative rather than qualitative, and we believe that all suffered from the same fundamental tissue injury following their streptococcic infection; namely, that characteristic of rheumatic fever.

AUTHORS.

Martiarena, L. H.: Secondary Tumor of the Heart Diagnosed at Operation, *Rev. argent. de cardiol.* 12: 13, 1945.

A case is reported of secondary heart tumor with clinical signs of cardiac involvement which was diagnosed as a constrictive pericarditis. Roentgen-ray examination of the lungs did not show parenchymatous alterations; nevertheless in the operation a tumor of bronchial origin was found, which was hidden by a shadow of right pleural effusion. In the operation the strong adhesions found between lung and diaphragm prevented the liberation of the heart. Post-mortem examination showed a tumor of the right lung that had invaded secondarily the right and part of the left auricle, which was recognized as an epithelioma of bronchial origin.

AUTHOR.

Herztein, J., and Weinroth, L. A.: Arteriosclerotic Peripheral Vascular Disease in Diabetes, *Arch. Int. Med.* 76: 34, 1945.

Confirming the work of others, our observations indicate that an apparently selective and frequently premature arteriosclerosis occurs in the peripheral vessels of the lower extremities in diabetic patients.

The increased incidence of arteriosclerosis in diabetic patients, irrespective of the usually accepted factors which determine arteriosclerosis in nondiabetic persons, may indicate a metabolic origin or imply an acceleration of the process by some metabolic factor. From the statistical standpoint of our study, the relationship between such factors and peripheral vascular disease is not made evident.

The presence of cholesterol deposits in the arteriosclerotic lesion and the hypercholesterolemia of patients with neglected or poorly controlled diabetes suggest a linkage between the two disorders. However, no such connection has so far been unequivocally established. It does not, of course, follow that in the treatment of diabetes such factors as control of weight and hypertension can be ignored or that suitable dietary and insulin regimens can be neglected.

AUTHORS.

Gregory, R., Ewing, P. L., Levin, W. C., and Ross, G. T.: Studies on Hypertension, *Arch. Int. Med.* 76: 11, 1945.

The vasoconstrictor effect of angiotonin can be detected in perfusions of whole pithed frogs.

Angiotonin may be ultrafiltrated and detected in blood plasma ultrafiltrates by this method of bioassay.

Angiotonin may be demonstrated in the ultrafiltrates of plasma from patients whose blood pressures have been elevated by intravenous injections of angiotonin.

Ultrafiltrates of blood plasma from normal and from hypertensive patients contain an almost identical amount of vasoconstrictor substance or substances.

Ultrafiltrates of blood plasma from patients made transiently hypertensive by angiotonin contain a much greater amount of vasoconstrictor substance than ultrafiltrates of plasma from hypertensive patients whose blood pressures are much higher.

Plotted curves of vasoconstrictor effects of ultrafiltrates of plasma from normotensive and from hypertensive persons are identical and differ greatly in character from curves of vasoconstrictor effects of angiotonin in frog Ringer solution or in ultrafiltrates of blood plasma to which angiotonin has been added.

Angiotonin is not present in increased amounts in the blood of patients with essential hypertension of long duration.

In essential hypertension of long duration, the elevation of blood pressure is not due to increased production of angiotonin. Essential hypertension is probably not caused by an increased production of angiotonin.

AUTHORS.

Gross, R. E.: Arterial Embolism and Thrombosis in Infancy, *Am. J. Dis. Child* 70: 61, 1945.

A study was made of forty-seven patients, including six of my own, who had arterial thrombosis or embolism in early life, principally in the neonatal period. The origin of the occlusion was often obscure, but in some cases it was apparently caused by trauma, infection, embolism from aseptic cardiac vegetations or abnormal clotting in the presence of polycythemia. I should particularly like to draw attention to two additional mechanisms whereby arterial vascular accidents can be produced in babies. With the first, the thrombosis of the umbilical arteries extends beyond the expected normal range so that the clot extended into the pelvic arteries or into the lower portion of the aorta. With the second, a closing ductus arteriosus may be the seat of thrombus formation, from which emboli can be thrown off into the pulmonary or the peripheral circuit.

In infants, arterial obstruction was found in the brain, the kidneys, the mesentery, the lungs, the arms, and, especially the legs. The prognosis for many of these subjects is serious: One-half of the patients in the series died. Fatalities which are secondary to cardiac disorders will probably always be unavoidable, but death from secondary sepsis can often be prevented by adequate care of an affected limb, by use of sulfonamide compounds and penicillin, and by amputation when necessary.

It is important to note that ischemia of an extremity does not necessarily mean that the part will die or that early amputation will be required. Occlusion of a large artery may at first seem incompatible with survival of the limb, but experience has shown that the collateral vessels of a baby have an extraordinary capacity for maintaining the blood flow. Hence, amputation should be deferred as long as is expedient; secondary infection should be carefully prevented, and every effort should be made to augment the impaired circulation. If an ischemic limb can be tided over its period of initial insult, there is a fairly good chance that it will survive and will regain satisfactory function. .

AUTHOR.

Selzer, A.: Circulation in Acute Myocardial Infarction, *Arch. Int. Med.* 76: 51, 1945.

Forty-five unselected patients with acute myocardial infarction were studied by serial determination of the arm-to-tongue circulation time and twenty-two of them also by serial determinations of vital capacity. The results were correlated with the clinical observations and with the course of the disease.

In all but three patients the initial readings of the circulation time were above normal, the average value for the series being 24.3 seconds (normal 13 seconds). In twenty-four of the thirty-two patients who recovered clinically there was a significant decrease in the circulation time on subsequent readings.

Prolonged circulation time indicating left ventricular failure was found most definitely in patients with clinical evidence of cardiac insufficiency (nineteen patients with an average value of 28 seconds); however, in patients who were entirely asymptomatic except for pain, there was still a definite delay, indicating latent left ventricular failure (twenty-six patients with an average of 21.4 seconds).

Determinations of circulation time are of practical value and are thought to be worth while as a routine procedure in myocardial infarction (a) as an aid in diagnosis by helping to differentiate it from other conditions associated with pain in the chest and (b) in evaluating the progress of circulatory readjustment after an infarction by means of repeated determinations of circulation time.

AUTHOR.

Taylor, H. L., Erickson, L., Henschel, A., and Keys, A.: The Effect of Bed Rest on the Blood Volume of Normal Young Men, *Am. J. Physiol.* 144: 227, 1945.

1. The effect of three weeks of complete bed rest on the blood volume and its component parts has been studied in six experiments on five normal young men. In four men, studies were carried out during the course of reconditioning. In addition, one of these men was studied before and after the surgical repair of an inguinal hernia.

2. An average loss in blood volume of 572 ml., or 9.3 per cent, occurred during the period of bed rest. This was almost entirely accounted for by a contraction of the plasma volume of 518 ml., or 15.5 per cent.

3. The first week of reconditioning resulted in an increase in plasma volume to prebed rest levels but was accompanied by an apparent loss of red cells so that the average increase of blood volume was only 235 ml. The subsequent apparent increase in blood volume to the original level was due entirely to an increase in red blood cells.

4. The blood volume change after the surgical repair of an inguinal hernia and three weeks' bed rest in one man did not differ significantly from the changes observed in the same man after simple bed rest alone.

5. Correlations between blood volume changes and various indices of deterioration of cardiovascular function are discussed. AUTHORS.

Moia, B.: Treatment of Night Cramps and the So-Called Vasomotor Neurosis of the Extremities With Quinine, *Rev. argent. de cardiol.* 11: 376, 1945.

The syndrome described by Nothnagel as angina pectoris vasomotoria is described showing that it has nothing in common with angina pectoris and that it is only a clinical form of the so-called vasomotor neurosis. Considering the many points of contact between this syndrome and the night cramps of the extremities the author treated it with quinine.

As previously recommended for the latter, the author administered 0.20 Gm. of quinine sulphate per os, at night, before bedtime, to thirty women between 38 and 59 years of age. In all these cases vasodilator drugs and other treatments, including those which improved coexistent hypertrophic arthritis, had been ineffective.

Great improvement was obtained in 70.3 per cent of cases. After withdrawal of the drug, improvement persisted until about twenty days; on recurrence of symptoms the re-administration of quinine was again effective.

The etiopathogenic relations between the vasomotor neurosis of the extremities and the night cramps are discussed as well as the mechanism of action of quinine. AUTHOR.

Holzmann, M., and Spuhler, O.: Infarct Electrocardiogram and Veronal Poisoning, *Cardiologia* 6: 225, 1942.

In a case of old posterior wall infarct, the appearance of an electrocardiogram of the early stage type was observed during veronal poisoning, without new infarction. This shows that this electrocardiograph type, in the case of localized coronary circulatory disturbance, may be produced not only by overwork by a blood pressure crisis or by an acute ischemia, but also by acute toxic cellular metabolic disturbance. AUTHORS.

Murphy, G. E.: Salicylate and Rheumatic Activity, *Bull. Johns Hopkins Hosp.* 127: 1, 1945.

An objective study of the clinical course and histologic character of rheumatic lesions in twelve actively rheumatic patients treated with large doses of salicylate was carried out. In six patients the size of involved joints and in six patients size and skin temperature of involved joints were followed by direct measurement in an attempt to determine the effect of salicylate upon the local rheumatic inflammation. The results in this small series of cases do not support the widely accepted view that salicylate promotes the subsidence of the rheumatic joint inflammation. In several of these patients characteristic rheumatic lesions developed in a variety of sites during the course of salicylate therapy. In two cases tendon sheath nodules developed; with another case a tenosynovitis developed with the serum salicyl level between 300 and 450 gammas per cubic centimeter, respectively. In another case the tenosynovitis developed with the serum salicyl level between 350 and 265 gammas per cubic centimeter. A florid rheumatic pneumonitis appeared to develop in a fatal case with the serum salicyl level above 300 gammas per cubic centimeter, another striking finding at autopsy in this case being fresh fibrin thrombi in capillaries of practically every glomerulus in sections of both kidneys. In a fifth patient an episcleral nodule developed with the serum salicyl level between 450 and 600 gammas per cubic centimeter. The histology of these lesions is illustrated and described. A review of the literature pertaining to episcleral and scleral lesions developing in the course of active rheumatic fever and evidence for considering the episcleral lesion in the present studies of rheumatic nature are presented. In a sixth patient joint rheumatic activity became manifest for the first time during the course of heavy salicylate therapy (after fifteen days of large doses of salicylate) associated with electrocardiographic evidence of increased cardiac rheumatic activity. AUTHOR.

Rich, A. R.: Hypersensitivity to Iodine as a Cause of Periarthritis Nodosa, *Bull. Johns Hopkins Hosp.* 77: 43, 1945.

Previous studies have demonstrated that anaphylactic hypersensitivity to foreign serum and to sulfonamides can cause periarthritis nodosa. The present report adds iodine to the

sensitizing substances that can cause this destructive vascular lesion, and emphasizes that substances of widely different chemical nature have this potentiality, depending upon their ability to induce the state of anaphylactic hypersensitivity. AUTHOR.

Wedd, A. M., and Blair, H. A.: The Effect of Barium Chloride on the Heart, *J. Lab. & Clin. Med.* 30: 765, 1945.

The effect of barium chloride on the whole auricle and on strips of ventricle of the turtle heart has been studied. The principal action of the drug was to increase rhythmicity. This effect was more marked when the rate of beating was relatively low, and also when the tissue had been removed from the animal for twenty-four or more hours. Contractility was usually depressed. The influence on excitability, measured by the Q-T of the electrogram, and on muscle fiber conduction was slight. AUTHORS.

Steinberg, F., and Jensen, J.: On the Use of Theophylline Aminoisobutanol in Angina Pectoris, *J. Lab. & Clin. Med.* 30: 769, 1945.

There is no significant absence of attacks of angina pectoris during the periods when the patients received theophylline aminoisobutanol as contracted with the periods when they received the inert substance or no drug at all. It is concluded that theophylline in general, and specifically theophylline aminoisobutanol, exerts no demonstrable effect upon the incidence of attacks in patients with angina pectoris. AUTHORS.

Raab, W.: Diminution of Epinephrine Sensitivity of the Normal Human Heart Through Thiouracil, *J. Lab. & Clin. Med.* 30: 774, 1945.

Thiouracil administration for three months to ten physically healthy persons was followed by a significant diminution of the sensitivity of the heart to epinephrine (heart rate, electrocardiogram). The behavior of the blood pressure was rather uncharacteristic. Implications of these observations regarding the pathogenesis and treatment of angina pectoris are briefly discussed. AUTHOR.

Guerra, F., and Chavez, N.: Value of Iontophoresis With Sodium Salicylate in Cardiovascular Rheumatism, *Arch. Inst. cardiol. México* 15: 153, 1945.

Following intravenous injection of 1 Gm. of a 10 per cent sodium salicylate solution per 50 kg. body weight after ten minutes a level of 150 ± 17 micrograms per cubic centimeter of salicylicion in blood serum was obtained.

After ion transfer with 2 to 4 per cent sodium salicylate solution with 5 to 10 milliamperes during fifteen to thirty minutes in the precordial region no traces of salicylicion were present in the blood.

The drug concentrations of the solution before and after the ion transfer were the same.

The claims of clinical improvement in cardiovascular rheumatism following ion transfer with sodium salicylate are, therefore, not due to the presence of the drug in blood or to its specific action upon rheumatism. AUTHORS.

Allmark, M. G., and Bachinski, W. M.: Present Status of the Standardization of Digitalis and Strophanthus Products in Canada, *Canad. M. A. J.* 53: 361, 1945.

The purpose of this paper from the laboratory of Hygiene, Department of National Health and Welfare, Ottawa, is to present a report on the comparative assays for standardization of digitalis, and to discuss the responsibility of the Department of National Health and Welfare as a regulatory body in connection with standardization of these products in Canada.

Canadian pharmaceutical companies would obtain more uniformity in potency for both digitalis and strophanthus preparations if the U.S.P. XII cat method was employed to standardize their products.

Digitalis products which are not reproducible from batch to batch and from which no national standards are available should be standardized by a biological method, and a standard used which is qualitatively the same as the samples tested.

Preparations like digitalin (crystalline) should not be labeled in International Units. The human requirements of digitalin are considerably less than the potency ratio between digitoxin and digitalis on cats would indicate. McCULLOCH.

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INDEX TO VOLUME 30

A

- Abell, R. G., Chambers, R., Clowes, G. H. A., and Zweifach, B. W., 212*
- Acetylcholine, stimulating effect of, on mammalian heart and liberation of an epinephrine-like substance by isolated heart, 627*
- Acevedo, H. J., and Moia, B., 532*
- Adrenalin, study of body temperature and water content in shock produced by continuous intravenous injection of, with or without anesthesia, 106*
- Adults, young, traumatic rupture of normal aorta in, 321
- Age, older group, with coronary arteriosclerosis and hypertension, effect of smoking cigarettes on peripheral blood flow in subjects in, 541
relation of, and other factors to cardiac subendothelial hemorrhage in dogs, 592
- Ageing, influence of, in man upon his capacity for physical work and upon his cardiovascular response to exercise, 102*
- Air, cold, effects of, on air passages and lungs, 101*
- Alexander, H. L., and Wilson, K. S., 210*
- Alexander, R. S., 314*
- Allmark, M. G., and Bachinski, W. M., 633*
- Aminophylline (*See* Ethylenediamine)
- Amyl nitrite, effects of, on downward T wave of electrocardiogram, 60
measurement of lung-to-face time by, 19
- Anemia, chronic, as measured by technique of right atrial catheterization, cardiac output in patients with, 420*
- Anesthesia and environmental temperature, effect of, on survival of tourniquet shock in rabbits, 106*
sodium pentobarbital, effect of sulfadiazine, antitoxins, globulins, and dog plasma on dogs in traumatic shock under, 106*
study of body temperature and water content in shock produced by continuous intravenous injections of adrenalin, with or without, 106*
- Aneurysm, arteriovenous, modification of respiration and circulation in, 211*
cardiac, with rupture, 133
spontaneous, 567
congenital arteriovenous, 209*
mycotic, death from rupture of; case of infection with *Brucella suis*, causing endocarditis and nephritis, 77
periarteritis nodosa producing, of the renal artery and hypertension, 211*
pulmonary artery, hemorrhagic telangiectasia with, 534*

- Angina pectoris associated with dextrocardia and situs inversus, 202
on use of theophylline aminoisobutanol in, 633*
with particular reference to its occurrence before and after myocardial infarction, 599
- Announcement, 425, 539
- Anomalies, genitourinary and associated vascular, aortic hypoplasia with, 514
- Anomaly, congenital, angina pectoris associated with dextrocardia and situs inversus, 202
arteriovenous aneurysms, 209*
coarctation of aorta, relating clinical data to degree of constriction measured at autopsy, with a method of standardization for related measurements, 30
cor triloculare bicaudate, 209*
interventricular septal defect (Roger's disease) occurring in mother and her six-month fetus, 54
large interauricular septal defect with particular reference to diagnosis and longevity, 103*
- Anoxia and blood flow, effects of, on spinal cardiovascular centers, 314*
- Antitoxins, globulins, sulfadiazine, and dog plasma, effect of, on dogs in traumatic shock under sodium pentobarbital anesthesia, 106*
- Anxiety and tilting, normal values with observations on effect of; cardiac output in male subjects as measured by technique of right atrial catheterization, 315*
- Aorta, coarctation of; relating clinical data to degree of constriction measured at autopsy, with method of standardization for related measurements, 30
hypoplasia of, with associated vascular and genitourinary anomalies, 514
normal, in young adults, traumatic rupture of, 321
simplified technique for removal of saddle embolus at bifurcation of, with report of successful case; arterial embolism, 107*
- Aortic atresia or marked hypoplasia of aorta at its base, clinical and pathological findings in, 209*
- Armstrong, C. D., Kirby, W. M. M., and Bloomfield, A. L., 423
- Arrillaga, F. C., 424*
- Arsenotherapy, intensive, electrocardiographic changes in early syphilis prior to and upon completion of, 551
- Arteriosclerosis, coronary, and myocardial infarction as studied by injection technique, 210*

- Artery, coronary arteriosclerosis and hypertension, effect of smoking cigarettes on the peripheral blood flow in subjects in older age group with, 541
and myocardial infarction as studied by injection technique, 210*
disease of, rupture of ventricular myocardium, with comments on clinical significance of possibility of, 39
occlusion of, and transient heart block in pleural shock, 423*
system with neoprene latex, demonstration of, 212*
disease, generalized, in Negroes, new form of, 390
embolism of; simplified technique for removal of saddle embolus at bifurcation of aorta with report of successful case, 107*
pulmonary, aneurysm of, hemorrhagic telangiectasia with, 534*
sclerosis and right heart failure, primary alveolar cell carcinoma of lung with, 309
renal, and hypertension, periarteritis nodosa producing aneurysm of, 211*
- Arthritis, postscarlatinal, and carditis, relationship of, to rheumatic fever, 629*
- Ashman, R., Ferguson, F. P., Gremillion, A. L., and Byer, E., 208*
- Askey, John Martin, and Neurath, O., 253
- Asthenia, neurocirculatory, studies concerning pathogenesis and etiology of; II. Mechanisms underlying giddiness found in patients with neurocirculatory asthenia, 325
III. Cardiovascular manifestations of neurocirculatory asthenia, 478
IV. Respiratory manifestations of neurocirculatory asthenia, 557
- Asthma, bronchial, and other forms of human hypersensitiveness, relation of periarteritis nodosa to, 210*
- Auricle, left, primary tumor of, simulating mitral stenosis, 230
output in normal subjects with observations on acute circulatory collapse in three instances, effect of venesection and pooling of blood in extremities on atrial pressure, and, 421*
right catheterization, technique of cardiac output in male subjects as measured by; normal values with observations on effect of anxiety and tilting, 315*
technique of right, catheterization, cardiac output in patients with chronic anemia as measured by, 420*
- A-V nodal rhythm with varying A-V block, unusual case of, 208*
- Axis, medium manifest, of unipolar derivation of extremities, determination of, 208*
systems, six, with application to vector AvT in ventricular hypertrophy, 208*
- B
- Bachinski, W. M., and Allmark, M. G., 633*
- Bain, C. W., 107*
- Baker, Hillier, L., Jr., Mokotoff, R., Mokotoff, G., and Katz, L. M., 215
- Barber, Donn J., and Stein, I., 118
- Barium chloride, effect of, on heart, 633*
- Barnes, A. R., Essex, H. E., and Pruitt, R. D., 422*
—, and May, R. M., 65
- Barnes, M. W., Joliffe, L. S., Finland, M., and Parker, F., Jr., 104*
- Bauer, Donald deF., and Iverson, L., 30
- Baum, Harry, Dimond, G., and Bond, G., 194
- Beggenstoss, A. H., Call, J. D., and Merritt, W. A., 104*
- Benatt, A. J., and Berg, W. F., 579
- Bennett, A. W., and Greene, J. A., 415
- Bereonsky, I., and Cossio, P., 629*
- Berg, W. F., and Benatt, A. J., 579
- Berger, Knute E., and Reed, L. K., 622
- Berk, Lionel, and Sapeika, N., 365
- Bernheim, syndrome of, 427
- Betsch, William F., 567
- Black, W. A., and Karpovich, P. V., 627*
- Blair, H. A., and Wedd, A. M., 633*
- Blood, arterial, after intravenous injection of labeled corpuscles, dilution curve of activity in, 1
flow and anoxia, effects of, on spinal cardiovascular centers, 314*
coronary, control of, in denervated isolated heart and heart-lung preparation of dog, 317*
in upper extremity, venous pressure as index of, 210*
peripheral, in subjects in older age group with coronary arteriosclerosis and hypertension, effect of smoking cigarettes on, 541
venous, in inferior vena cava, influence of abdominal and thoracic pressure upon, 315*
- pooling of, in extremities, and venesection, effect of, on atrial pressure and cardiac output in normal subjects with observations on acute circulatory collapse in three instances, 421*
- pressure in inferior vena cava, intraabdominal pressure and, 420*
transient "0" diastolic brachial (indirect), associated with normal or elevated popliteal pressure, tachycardia, and nervous tension, 381
venous as index of blood flow in upper extremity, 210*
- vessels, injection technique, coronary arteriosclerosis and myocardial infarction as studied by, 210*
major, of lower extremity, experience with lumbar sympathetic ganglionectomy for wounds of, 534*
peripheral, in tourniquet shock, role of decompensatory reactions of, 212*

Blood—Cont'd

- volume deficiency, treatment of hemorrhagic shock irreversible to replacement of (x); traumatic shock, 535*
- deformations with radioactive phosphorus, 318*
- of normal young men, effect of bed rest on, 631*
- Bloom, Nathan, and Cashion, G., 619
- Bloomfield, A. L., Armstrong, C. D., and Kirby, W. M. M., 423*
- Body fluids of dogs in traumatic shock, distribution of, 213*
- temperature and water content in shock produced by continuous intravenous injection of adrenalin, with or without anesthesia, study of, 106*
- Bond, George, Baum, H., and Dimond, G., 194
- Book reviews:
- Electrocardiography, primer of, 537
- Heart, disease of, 425
- Voluntary health agencies, 425
- Borts, Irving H., DeGowin, E. L., and Carter, J. R., 77
- Bourne, G., 319*
- Bradycardia, sinus, with cardiac arrest, 316*
- Brain abscess associated with congenital heart disease, 209*
- Brannon, E. S., Merrill, A. J., Warren, J. V., and Stead, E. A., Jr., 315,* 420,* 421*
- Brodsky, M. B., Rodriguex, G. C., Del Solar, A. V., and Dussailant, G. G., 213*
- Brown, Halla, Stewart, H. J., and Haskell, H. S., 541
- Brucella*, endocarditis due to, 104*
- suis*, case of infection with, causing endocarditis and nephritis; death from rupture of mycotic aneurysm, 77
- Burch, George, and Winsor, T., 537 (B. rev.)
- Burrett, J. B., and White, P. D., 103*
- Burton, C. R., 259
- Byer, E., Ashman, R., Ferguson, F. P., and Gremillion, A. I., 208*

C

- Cabrera, E., and Pallares, S. D., 208*
- , —, and Cuellar, A., 208*
- , Vizcaino, M., and Pallares, D. S., 421*
- Cain, J. C., 202
- Calcification, annulus fibrosus, of mitral valve, 619
- Calef, Benson, and Saland, G., 398
- Cal, J. D., Beggenstoss, R. H., and Merritt, W. A., 104*
- Cameron, D. R., 423*
- Campbell, William A., and McDonald, J. B., 321
- Canabal, Eduardo Joaquin, Warneford-Thomson, H. F., and White, P. D., 189
- Canada, present status of standardization of digitalis and strophanthus products in, 633*

- Carcinoma, primary alveolar cell, of lung with pulmonary artery sclerosis and right heart failure, 309
- Cardiovascular centers, spinal, effects of blood flow and anoxia on, 314*
- damage done, reversibility of, by nearly complete exsanguination, 534*
- manifestations of neurocirculatory asthenia (III); studies concerning the etiology and pathogenesis of neurocirculatory asthenia, 478
- response to exercise, influence of aging in man upon his capacity for physical work and upon, 102*
- rheumatism, value of iontophoresis with sodium salicylate in, 633*
- Cardioelectrography, principle of, 532*
- Carditis and postscarlatinal arthritis, relationship of, to rheumatic fever, 629*
- Carter, John R., Borts, I. H., and DeGowin, E. L., 77
- Cashion, Grace, and Bloom, N., 619
- Cerberin, clinical observation with, 194
- Chambers, R., Clowes, G. H. A., Zweifach, B. W., and Abell, R. G., 212*
- Chapman, Don W., 276
- Chavez, N., and Guerna, F., 633*
- Children, overweight and adolescent, significance of erythrocyte sedimentation rate in rheumatic fever in, 533*
- salicylate therapy in rheumatic fever in, 424*
- Cigarettes, effect of smoking, on the peripheral blood flow in subjects in older age group with coronary arteriosclerosis and hypertension, 541
- Circulation and respiration in arteriovenous aneurysm, modification of, 211*
- bilateral, venous occlusion of hind-limbs of dog, observations on shock following, 212*
- collapse, acute, in three instances, effect of venesection and pooling of blood in extremities on atrial pressure and cardiac output in normal subjects with observations on, 421*
- coronary, insufficiency of, revealed by ectopic, nodal, and ventricular beats in presence of left bundle branch block, 209*
- in acute myocardial infarction, 631*
- postocclusive collateral, primary influence of basal vascular tone on development of, and in selecting patients for sympathectomy, 107*
- time, determination of; unsuitability of papaverine, 363
- dilution curve of activity in arterial blood after intravenous injection of labeled corpuscles, 1
- lung-to-face, measurement of, by amyl nitrite, 19
- City of Mexico, frequency of congenital anatomic lesions of heart in, 316*
- Clowes, G. H. A., Zweifach, B. W., Abell, R. G., and Chambers, R., 212*

- Coarctation of aorta; relating clinical data to degree of constriction measured at autopsy with method of standardization for related measurements, 30
- Condenser field, modulated high-frequency, effect of, on Straub-Fuehner frog heart preparation, 420*
- Conduction system, total, sinus extrasystole with consecutive disturbance of condition in, 628*
- Cookson, H., 316*
- Cor triloculare biauriculare, 209*
- Corpuscles, labeled, dilution curve of activity in arterial blood after intravenous injection of, 1
- Cossio, P., and Berconsky, I., 629*
- Costa Rica and New York, relative incidence of rheumatic valve disease in, and its bearing on rheumatic origin of calcareous aortic stenosis, 573
- Costero, and Fuertes, G. A., 316*
- Cramps, night, and so-called vasomotor neurosis of extremities, treatment of, with quinine, 632*
- Crede, Robert H., and Klotz, S. D., 551
- Cruikshank, R., and Dolphin, A., 423*
- Cuellar, A., Cabrera, E., and Pallares, S. D., 208*
- Currens, James H., Kinney, T. D., and White, P. D., 491
- Cycle-length changes, effect of, upon form and amplitude of T deflection of electrocardiogram, 208*

D

- Dawson, P. M., and Hellebrandt, F. A., 102*
- Death, unexpected, laryngeal edema, and myocarditis, 628*
- DeGowin, Elmer L., Carter, J. R., and Borts, I. H., 77
- Del Solar, A. V., Dussailant, G. G., Brodsky, M. B., and Rodriguex, G. C., 213*
- DeKruif, P., Simpson, W. M., Kendell, H. W., Rose, D. L., Gottschall, R. Y., and Laurent, D., 536*
- Dermatomyositis, peripheral vascular changes in, 441
- Dextrocardia and situs inversus, angina pectoris associated with, 202
- Diabetes, arteriosclerotic peripheral vascular disease in, 630*
- Diaz, Marcial Fallas, Wilens, S. L., and Pearce, J. M., 573
- Diet, thiamine-deficient, in tourniquet shock in rats, 106*
- Digitaline "Nativelle," and digitalis leaf, oral single-dose digitalization with, 125
- Digitalis and strophanthus products in Canada, present status of standardization of, 633*
- epinephrine, and surgery, effect of, on response to heparin, 319*
- folia, intravenous administration of lanatoside C to patients taking maintenance doses of, up to

Digitalis—Cont'd

- date of hospitalization with recent congestive heart failure, 335
- indicated in myocardial infarction, 533*
- leaf and digitaline "Nativelle," oral single-dose digitalization with, 125
- Dilution curve of activity in arterial blood after intravenous injection of labeled corpuscles, 1
- Dimond, G., Bond, G., and Baum, H., 194
- Diphtheria, auricular fibrillation and auricular flutter in, 315*
- heart block, and simulation of bundle block in, 316*
- following, 422*
- Dock, William, 332
- Dolphin, A., and Cruikshank, R., 423*
- Donovan, Maurice A., Simon, H., and Field, M. H., 230
- Duchosal, P. W., and Sulzer, R., 532*
- Ductus arteriosus, patent, ligation of, 319*
- ligature of, 319*
- observations on ligation of, 536*
- Duncan, G. W., 210*
- Duomarco, J., Recrate, P., and Rimini, R., 315,* 420*
- Dussailant, G. G., Brodsky, M. B., Rodriguex, G. C., and Del Solar, A. V., 213*

E

- Eagan, John C., 610
- East, T., 319*
- Edema, laryngeal, myocarditis, and unexpected death, 628*
- Eisaman, Jack L., 401
- Electrocardiogram, effects of amyl nitrite on downward T wave of, 60
- of cycle-length changes upon form and amplitude of T deflection of, 208*
- in hypertension; I. Its description, 140
- II. Effect of radical lumbodorsal sympathectomy, 165
- III. Electrocardiograms of hypertensive patients followed for long time without splanchnic resection in comparison with those in patients who had had splanchnic resection, 189
- in pneumoperitoneum, 579
- infarct, and veronal poisoning, 632*
- P-R interval in rheumatic fever, provocative prolongation of, 104*
- precordial, changes in, produced by extension of antero-septal myocardial infarction, 11
- type S₁ S₂ S₃, certain considerations concerning, 421*
- Electrocardiograms simulating posterior myocardial infarction after cessation of paroxysmal tachycardia, 401
- Electrocardiographic changes associated with lesions in deeper layers of myocardium, 422*
- in early syphilis prior to and upon completion of intensive arsenotherapy, 551

Electrocardiographic—Cont'd

- diagnosis of myocardial infarction complicated by branch block, 532*
 - features of myocardial infarction as affected by involvement of septum and by complete and incomplete transmural involvement, 367
 - localization of myocardial infarcts by injury currents and ventricular extrasystoles, 421*
 - patterns, basic, in bundle branch block, 102*
- Electrogram of cardiac ventricle, interpretation of, 314*
- Embarazo, Cirugia Y, 425 (B. rev.)
- Embolic or thrombotic processes, incidence of, during immediate convalescence from acute myocardial infarction, 65
- Embolism, arterial, and thrombosis in infancy, 631*
- simplified technique for removal of saddle embolus at bifurcation of aorta with report of successful case, 107*
- Endocarditis, acute bacterial, penicillin therapy in, 423*
- and nephritis, case of infection with *Brucella suis*, causing; death from rupture of mycotic aneurysm, 77
 - due to *Brucella*; report of two cases, 104*
 - healed subacute bacterial, 533*
 - note on serologic classification of streptococci isolated from subacute bacterial, 511
 - strains of *Streptococcus viridans*, enterococci, and Group A streptococci, effect of temperature elevation on action of sulfathiazole upon (II); pathology and bacteriology of streptococcus endocarditis in relationship to sulfonamide chemotherapy, 104*
 - streptococcus, pathology and bacteriology of, in relationship to sulfonamide chemotherapy; I. Development of laboratory technique for study of chemotherapy in vitro, 104*
 - II. Effect of temperature elevation on action of sulfathiazole upon endocarditis strains of *Streptococcus viridans*, enterococci, and Group A streptococci, 104*
 - subacute bacterial, immunologic studies in patients with, treated by combined penicillin-heparin method, 316*
 - treatment of, with penicillin, 423*
- Endocardium, valvular, histologic structure of, 628*
- Enterococci, *Streptococcus viridans*, and Group A streptococci, effect of temperature elevation on action of sulfathiazole upon endocarditis strains of (II); pathology and bacteriology of streptococcus endocarditis in relationship to sulfathiazole chemotherapy, 104*
- Enzer, N., and Simonson, E., 208*
- , —, and Goodman, J. S., 209*

- Epinephrine sensitivity of normal human heart, diminution of, through thiouracil, 633*
- surgery, and digitalis, effect of, on response to heparin, 319*
- Epstein, Bernard S., Grayzel, D. M., and Fishman, A. P., 309
- Erickson, L., Henschel, A., Keys, A., and Taylor, H. L., 631*
- Erythrocytes, effect of sodium salicylate on sedimentation rate of, in vitro, 533*
- Essex, H. E., Pruitt, R. D., and Barnes, A. R., 422*
- Ethylenediamine (aminophylline), effect of theophyllin with, and of papaverine hydrochloride on experimental myocardial infarction in dog, 215
- Evans, Elwyn, Mathews, M., and White, P. D., 140
- , —, —, and Smithwick, R. H., 165
- Ewing, P. L., Levin, W. C., Ross, G. T. and Gregory, R., 630*
- Exercise, effect of, upon erythrocyte sedimentation rate, 627*
- influence of aging in man upon his capacity for physical work and upon his cardiovascular responses to, 102*
- Exsanguination, nearly complete, efficacy of gelatin solutions and other cell-free fluids in reversing effects of, 535*
- reversibility of cardiovascular damage done by, 534*
- Extrasystole, sinus, with consecutive disturbance of conduction in total conduction system, 628*
- Extrasystoles, ventricular, and injury currents, electrocardiographic localization of myocardial infarcts by, 421*

F

- Fenning, C., and Mott, C. R., 420*
- Ferguson, F. P., Gremillion, A. I., Byer, E., and Ashman, R., 208*
- Fetus, complete A-V block in, 615
- six-month, and mother, interventricular septal defect (Roger's disease) occurring in, 54
- Fever, artificially introduced, effect of, on humoral antibodies and on histamine intoxication in guinea pig, 536*
- Fibrillation, auricular, and auricular flutter in diphtheria, 315*
- occurring with myocardial infarction, treatment of, 253
 - permanent, in two brothers without evidence of organic heart disease, 422*
- Fick procedure, determination of cardiac output in dog by, 420*
- Field, Miriam Hirschfeldt, Donovan, M. A., and Simon, H., 230
- Fine, J., Frank, H. A., and Seligman, A. M., 535*
- , and Goldberg, M., 536*

- Fink, K., Warren, S. L., and Ricca, R. A., 106*
- , —, —, and Katzin, L. I., 213*
- , —, —, and Steadman, L. T., 213*
- , —, Steadman, L. T., Scholz, D. E., Schultz, J. H., and Pleune, F. G., 106*
- Finland, M., Parker, F., Jr., Barnes, M. W., and Joliffe, L. S., 104*
- Fisher, Ralph Lee, 133
- Fishman, Alfred P., Epstein, B. S., and Grayzel, D. M., 309
- Fluids, body, of dogs in traumatic shock, distribution of, 213*
- Flutter, auricular, and auricular fibrillation in diphtheria, 315*
- Foley, G. E., and Wheeler, S. M., 511
- Foreign body, intracardiac, 88
- Frank, H. A., Seligman, A. M., and Fine, J., 535*
- Friedberg, L., and Katz, L. N., 212*
- Friedman, Burt, Simard, E. E., and Schwartz, I., 299
- Friedman, Meyer, 325, 478, 557
- Fuertes, G. A., and Costero, 316*
- Fullerton, C. W., 424*

G

- Gallop rhythm, so-called systolic, nature and origin of, 423*
- Ganglia stellate and cardiac nerves, cardiac response to stimulation of, 101*
- Ganglionectomy, lumbar sympathetic, for wounds of major blood vessels of lower extremity, experience with, 534*
- Gaspary, F. V., and Sabathie, L. G., 102*
- , —, and Rojas, R. A., 422*
- Geiger, Arthur J., and Goerner, J. R., 284
- Gelatin solutions and other cell-free fluids, efficacy of, in reversing the effects of nearly complete exsanguination, 535*
- Giddiness found in patients with neurocirculatory asthenia, mechanisms underlying. (II); studies concerning etiology and pathogenesis of neurocirculatory asthenia, 325
- Giddings, W. P., and Mason, J. M., III, 534*
- Ginsburg, H. N., Schiff, I., Krause, F., Katz, L. N., and Wise, W., 125
- Globulins, sulfadiazine, antitoxins, and dog plasma, effect of, on dogs in traumatic shock under sodium pentobarbital anesthesia, 106*
- Goerner, Jessamine R., and Geiger, A. J., 284
- Goldberg, M., and Fine, J., 536*
- Goldberger, Emanuel, 60, 102,* 341
- Goldenberg, Marcel, and Pardee, H. E. B., 367
- Gómez, B. H., and Yépez, C. G., 422*
- Goodman, J. S., Simonson, E., and Enzer, N., 209*
- Gottschall, R. Y., Laurent, D., DeKruif, P., Simpson, W. M., Kendell, H. W., and Rose, D. L., 536*

- Grayzel, David M., Fishman, A. P., and Epstein, B. S., 309
- Greene, James A., and Bennett, A. W., 415
- Gregg, E. D., and Shipley, R. E., 101*
- Gregory, R., Ewing, P. L., Levin, W. C., and Ross, G. T., 630*
- Gremillion, A. I., Byer, E., Ashman, R., and Ferguson, F. P., 208*
- Groedel, F. M., and Miller, M., 423*
- Grolnick, M., and Loewe, L., 316*
- Gross, Desiderio, 19
- Gross, R. E., 631*
- Gubner, R., Szucs, M., and Ungerleider, H. E., 104*
- Guerra, F., and Chavez, N., 633*
- Gunn, Selskar, and Platt, P. S., 425 (B. rev.)

H

- Hamilton, B. W., and Hamilton, T. R., 104*
- Hamilton, T. R., and Hamilton, B. W., 104*
- Hanson, James Fletcher, and Logue, R. B., 205
- Harris, T. N., 533*
- Haskell, Helen S., Brown, H., and Stewart, H. J., 541
- Heart, aneurysm of, with rupture, 133
- spontaneous, 567
- asystole, sinus bradycardia with, 316*
- block and simulation of bundle block in diphtheria, 315*
- branch, electrocardiographic diagnosis of myocardial infarction complicated by, 532*
- bundle branch, basic electrocardiographic patterns in, 102*
- complete, and pericarditis during thiouracil therapy, 107*
- A-V, in fetus, 615
- in German measles, 205
- following diphtheria, 422*
- incomplete, produced by changes in posture, 291
- left bundle branch, coronary insufficiency revealed by ectopic, nodal, and ventricular beats in presence of, 209*
- paroxysmal complete, produced by ischemia of auriculoventricular node, 238
- transient, and coronary occlusion in pleural shock, 423*
- in congenital heart disease, 92
- unstable auriculoventricular, permanent, residual, and benign, 102*
- intraventricular, 422*
- varying A-V, and unusual case of A-V nodal rhythm, 208*
- contusion of, 622
- denervated, isolated, and heart-lung preparation of dog, control of coronary flow in, 317*
- disease, acquired, significance of heredity for origin of, 532*
- acute rheumatic, in aged, with report of case with Stokes-Adams syndrome treated with paredrine, 415
- congenital, brain abscess associated with, 209*
- report of three members of family, 118
- transient heart block in, 92

Heart disease—Cont'd

- organic, permanent auricular fibrillation in two brothers without evidence of, 422*
- ectopic, nodal, and ventricular beats, coronary insufficiency revealed by, in presence of left bundle branch block, 203*
- effect of barium chloride on, 633*
- failure in isolated heart and heart-lung preparation, dynamic alterations in, 105*
- recurrent congestive, intravenous administration of lanatoside C to patients taking maintenance doses of folia digitalis up to date of hospitalization with, 335
- right, and pulmonary artery sclerosis, primary alveolar cell carcinoma of lung with, 309
- frequency of congenital anatomic lesions of, in City of Mexico, 316*
- infarction, value of Lead IVF in, 259
- isolated, and heart-lung preparation, dynamics of nonfailure period of, 317*
 - of dog, dynamics of, 211*
- stimulating effect of acetylcholine on mammalian heart and liberation of epinephrine-like substance by, 627*
- mammalian, stimulating effect of acetylcholine on, and liberation of epinephrine-like substance by isolated heart, 627*
- normal human, diminution of epinephrine sensitivity of, through thiouracil, 633*
- output and atrial pressure in normal subjects, effect of venesection and pooling of blood in extremities on, with observations on acute circulatory collapse in three instances, 421*
- in dog, determination of, by Fick procedure, 420*
- in male subjects as measured by technique of right atrial catheterization; normal values with observations of effect of anxiety and tilting, 315*
- in patients with chronic anemia as measured by technique of right atrial catheterization, 420*
- preparation, Straub-Fuehner frog, effect of modulated high-frequency condenser field on, 420*
- recruit's; reduplication of first sound, heart strain, and new method of calibration, 477
- response of, to stimulation of stellate ganglia and cardiac nerves, 101*
- secondary tumor of, diagnosed at operation, 630*
- sound, first and third, further evidence for purely valvular origin of, 332
 - reduplication of, heart strain and new method of calibration; recruit's heart, 447
- strain and new method of calibration, reduplication of first sound; recruit's heart, 447

Heart—Cont'd

- traumatic injury of; incidence of its occurrence in forty-two cases of severe accidental bodily injury, 459
 - rupture of both ventricles of, 519
- tumor; report of case, 411
- unusual primary leiomyosarcoma of, 299
- valve, rheumatic, relative incidence of, disease of, in New York and Costa Rica and its bearing on rheumatic origin of calcareous aortic stenosis, 573
- Heartbeat, normal, facts and fallacies about, 604
 - premature, of sinus origin; electrocardiographic demonstration of clinical case, 284
- Heart-lung preparations and isolated heart, dynamics of nonfailure period of, 317*
 - of dog, control of coronary flow in, 317*
 - dynamics of, 211*
- Hellebrandt, F. A., and Dawson, P. M., 102*
- Hemorrhage and replacement, effect of, on apparent volume of plasma and cells, 627*
- cardiac subendothelial, in dogs, relation of age and other factors to, 592
- Henry, M. J., and Smith, J. R., 212*
- Henschel, A., Keys, A., Taylor, H. L., and Erickson, L., 631*
- , and Visscher, M. B., 592
- Heparin, effect of digitalis, epinephrine, and surgery on response to, 319*
- Herbut, P. A., and Price, A. H., 211*
- Heredity, significance of, for origin of acquired heart disease, 532*
- Herztein, J., and Weinroth, L. A., 630*
- Hewlett, R. F. L., and Mehta, J. B., 209*
- Hillman, C. C., Levy, R. L., White, P. D., and Stroud, W. D., 534*
- Hines, L. E., and Kessler, D. L., 213*
- Histamine intoxication in guinea pig, humoral antibodies and, effect of artificially introduced fever on, 536*
- Hoff, H. E., and Nahum, L. H., 421*
- Hoffmann, E. J., Middleton, S., Talesnik, J., and Hoffmann, F., 627*
- Hoffmann, F., Hoffmann, E. J., Middleton, S., and Talesnik, J., 627*
- Holmes, Joseph H., and Weill, D. R., Jr., 291
- Holt, J. P., Knoefel, P. K., and Shore, R., 420*
- Holyoke, J. B., 210*
- Holzmann, M., and Spuhler, O., 632*
- Homburger, F., 533*
- Hunter, J. B., 536*
- Hypersensitiveness, human, relation of periarteritis nodosa to bronchial asthma and other forms of, 210*
 - studies on, 630*
 - transient, 534*
- Hypertension and aneurysm of renal artery, periarteritis nodosa producing, 211*

Hypertension—Cont'd

and coronary arteriosclerosis, effect of smoking cigarettes on peripheral blood flow in subjects in older age group with, 541
electrocardiogram in; I. Its description, 140

II. Effect of radical lumbodorsal sympathectomy, 165

III. Electrocardiogram of hypertensive patients followed for long time without splanchnic resection in comparison with those in patients who had had splanchnic resection, 189

fatal poisoning from potassium thiocyanate used in treatment of, 213*

I

Infancy, arterial embolism and thrombosis in, 631*

Infarct electrocardiogram and venous poisoning, 632*

Infarction, acute myocardial, circulation in, 631*

incidence of embolic or thrombotic processes during immediate convalescence from, 65

anteroseptal myocardial, changes in precordial electrocardiogram produced by extension of, 11

cardiac, value of Lead IVF in, 259

experimental myocardial, in dog, effect of theophyllin with ethylenediamine (aminophylline) and of papaverine hydrochloride on, 215

myocardial and coronary arteriosclerosis as studied by injection technique, 210*

angina pectoris with particular reference to its occurrence before and after, 599

complicated by heart block, electrocardiographic diagnosis of, 532*

electrocardiographic features of, as affected by involvement of septum and by complete and incomplete transmural involvement, 367

is digitalis indicated in, 533*

superimposed on short P-R, prolonged QRS complex, 527

treatment of auricular fibrillation occurring with, 253

posterior myocardial, after cessation of paroxysmal tachycardia, electrocardiograms simulating, 401

Infarcts, myocardial, electrocardiographic localization of, by injury currents and ventricular extrasystoles, 421*

Influenza A infections, acute myocarditis in, 104*

Injury currents and ventricular extrasystoles, electrocardiographic localization of myocardial infarcts by, 421*

Intraabdominal pressure and pressure in inferior vena cava, 420*

Iodine, hypersensitivity to, as cause of periarteritis nodosa, 632*

Iontophoresis with sodium salicylate, value of, in cardiovascular rheumatism, 633*

Ischemia of auriculoventricular node, paroxysmal complete heart block produced by, 238

Iverson, Lalla, and Bauer, D. deF., 30

J

Jacobs, M. H., and Taran, L. M., 424*

Jensen, J., and Steinberg, F., 633*

Jochim, K., Katz, L. N., and Wise, W., 105,* 211,* 317*

Johnson, R. S., and Lewes, D., 210*

Johnston, Franklin D., Rosenbaum, F. F., and Wilson, F. N., 11

Joliffe, L. S., Finland, M., Parker, F., Jr., and Barnes, M. W., 104*

K

Karpovich, P. V., and Black, W. A., 627*

Kartagener, M., 532*

Katz, L. N., and Friedberg, L., 212*

—, Mokotoff, R., Mokotoff, G., and Baker, H. L., 215

—, Wise, W., Ginsburg, H. N., Schiff, I., and Krause, F., 125

—, —, and Jochim, K., 105,* 211,* 317*

Katzin, L. I., and Warren, S. L., 106*

—, —, and Ricca, A. R., 106*

—, —, —, and Fink, K., 213*

Keith, J. D., and Ross, A., 424*

Kendell, H. W., Rose, D. L., Gottschall, R. Y., Laurent, D., DeKruif, P., and Simpson, W. M., 536*

Kessler, D. L., and Hines, L. E., 213*

Keys, A., Taylor, H. L., Erickson, L., and Henschel, A., 631*

Kinney, Thomas D., and Tucker, A. W., 54

—, White, P. D., and Currens, J. H., 491

Kirby, W. M. M., Bloomfield, A. L., and Armstrong, C. D., 423*

Klotz, Solomon D., and Crede, R. H., 551

Knoefel, P. K., Shore, R., and Holt, J. P., 420*

Krause, F., Ginsburg, H. N., Schiff, I., Katz, L. N., and Wise, W., 125

L

LaDue, John S., and Ray, T., 335

Lanatoside C, intravenous administration of, to patients taking maintenance doses of folia digitalis up to date of hospitalization with recurrent congestive heart failure, 335

Laurent, D., DeKruif, P., Simpson, W. M., Kendell, H. W., Rose, D. L., and Gottschall, R. Y., 536*

Lawson, H., and Rehm, W. S., 534,* 535,* 627*

Lead IVF, value of, in cardiac infarction, 259

Leiomyosarcoma, unusual primary, of heart, 299

Lepera, L., and Pataro, F. A., 628*

Letters, 531

- Levin, W. C., Ross, G. T., Gregory, R., and Ewing, P. L., 630*
- Levy, R. L., White, P. D., Stroud, W. D., and Hillman, C. C., 534*
- Lewes, D., and Johnson, R. S., 210*
- Lewis, J. Stephen, 447
- Leys, D. G., 422*
- Linton, R. R., 107*
- Loewe, L., and Grolnick, M., 316*
- , and Rosenblatt, P., 533*
- Logue, Robert Bruce, and Hanson, J. F., 205
- Lozada, B., and Taquini, A. C., 208*
- Lung, primary alveolar cell carcinoma of, with pulmonary artery sclerosis and right heart failure, 309
- Lungs and air passages, effects of cold air on, 101*

M

- McDonald, John B., and Campbell, W. A., 321
- Mannheimer, E., 532*
- Manning, G. W., and Stewart, C. B., 109
- Martirena, L. H., 630*
- Mason, J. M., III, and Giddings, W. P., 534*
- Mathews, Marion, White, P. D., and Evans, E., 140
- , —, —, and Smithwick, R. H., 165
- Mehta, J. B., and Hewlett, R. F. L., 209*
- Mendlowitz, Milton, 123
- Merrill, A. J., Brannon, E. S., Stead, E. A., Jr., and Warren, J. V., 315,* 420,* 421*
- Merritt, W. A., Call, J. D., and Beggenstoss, A. H., 104*
- Middleton, S., Talesnik, J., Hoffmann, F., and Hoffmann, E. J., 627*
- Miller, M., and Groedel, F. M., 423
- Moguel, R. B., 628*
- Moia, B., 632*
- , and Acevedo, H. J., 532*
- Mokotoff, Gertrude, Mokotoff, R., Katz, L. N., and Baker, H. L., 215
- Mokotoff, Reuben, Katz, L. N., Mokotoff, G., and Baker, H. L., 215
- Montenegro, Ovidio, and Pazzanese, D., 599
- Monto, Raymond W., and Woodall, P. S., 519
- Moses, C., 319*
- Mother and her six-month fetus, interventricular septal defect (Roger's disease) occurring in, 54
- Moritz, A. R., and Weisiger, J. R., 101*
- Mott, C. R., and Fenning, C., 420*
- Murphy, G. E., 632*
- , Newman, E. V., and Sisson, J. H., 209*
- Muscle, pectoralis minor, strain of, important cause of precordial pain in soldiers, 123
- Myocarditis, acute, in influenza A infections, 104*
- , isolated, probably of sulfonamide origin, 522
- , laryngeal edema, and unexpected death, 628*

- Myocardium, acute infarction of, circulation in, 631
- , electrocardiographic changes associated with lesions in deeper layers of, 422*
- , experimental infarction of, in dog, effect of theophyllin with ethylenediamine (aminophylline) and of papaverine hydrochloride on, 215
- , infarction of, acute, incidence of embolic or thrombotic processes during immediate convalescence from, 65
- , and coronary arteriosclerosis, as studied by injection technique, 210*
- , angina pectoris with particular reference to its occurrence before and after, 599
- , anteroseptal, changes in precordial electrocardiogram produced by extension of, 11
- , as affected by involvement of septum and by complete and incomplete transmural involvement, electrocardiographic features of, 367
- , complicated by branch block, electrocardiographic diagnosis of, 532*
- , superimposed on short P-R prolonged QRS complex, 527
- , treatment of auricular fibrillation occurring with, 253
- , infarcts of, electrocardiographic localization of, by injury currents and ventricular extrasystoles, 421*
- , is digitalis indicated in, 533
- , posterior, after cessation of paroxysmal tachycardia, electrocardiograms simulating, 401
- , ventricular, rupture of, comments on pathogenesis and on clinical significance of possibility of cardiac rupture in prognosis of coronary artery disease, 39

N

- Nahum, L. H., and Hoff, H. E., 421*
- Naide, M., and Sayen, A., 107*
- Nay, Richard M., and Barnes, A. R., 65
- Negroes, new form of generalized arterial disease in, 390
- Neoprene latex, demonstration of coronary arterial system with, 212*
- Nephritis and endocarditis, case of infection with *Brucella suis*, causing; death from rupture of mycotic aneurysm, 77
- Nerve, cardiac, and stellate ganglia, response to stimulation of, 101*
- , splanchnic resection, electrocardiograms of hypertensive patients followed for long time without, in comparison with those in patients who had had splanchnic resection (III); electrocardiogram in hypertension, 189
- Nervous tension, tachycardia, and normal or elevated popliteal pressure, and transient "0" diastolic brachial pressure (indirect) associated with, 381
- Neubauer, C., 315*
- Neurath, Otto, 533*

- , and Askey, J. M., 253
- Neurosis, so-called vasomotor, of extremities, and night cramps, treatment of, with quinine, 632*
- Newman, E. V., Sisson, J. H., and Murphy, G. E., 209*
- New York and Costa Rica, relative incidence of rheumatic valve disease in, and its bearing on rheumatic origin of calcareous aortic stenosis, 573
- Nicholl, Russell J., and Valentine, W. N., 514
- Niehaus, Frederick W., and Wright, W. D., 604
- Node, auriculoventricular, paroxysmal complete heart block produced by ischemia of, 238
- Nonfailure period of isolated heart and heart-lung preparation, dynamics of, 317*
- Nylin, G., 318
- Nylin, Gustav, 1

P

- Pain in episthenocardia pericarditis, 629*
precordial, in soldiers, strain of pectoralis minor muscle as important cause of, 123
- Pallares, D. S., Cabrera, E., and Vizcaino, M., 421*
- Pallares, S. D., and Cabrera, E., 208*
- , —, and Cuellar, A., 208*
- Papaverine hydrochloride and ethylenediamine (aminophylline), effect of theophyllin with, on experimental myocardial infarction in dog, 215
- unsuitability of, for determination of circulation time, 365
- Pardee, Harold E. B., and Goldenberg, M., 367
- Paredrine, acute rheumatic heart disease in aged, with report of a case with Stokes-Adams syndrome treated with, 415
- Parker, F., Jr., Barnes, M. W., Joliffe, L. S., and Finland, M., 104
- Pataro, F. A., and Lepera, L., 628*
- Pazzanese, Dante, and Nontenegro, O., 599
- Pearce, John M., Diaz, M. F., and Wilens, S. L., 573
- Pearson, R. S. B., 316*
- Penicillin therapy in acute bacterial endocarditis, 423*
treatment of subacute bacterial endocarditis with, 423*
- Penicillin-heparin method, combined, immunologic studies in patients with subacute bacterial endocarditis treated by, 316*
- Periarteritis episthenocardia, pain in, 629*
nodosa, 610
hypersensitivity to iodine as cause of, 632*
producing aneurysm of renal artery and hypertension, 211*
relation of, to bronchial asthma and other forms of human hypersensitiveness, 210*

- Pericarditis and complete heart block during thiouracil therapy, 107*
segmentary, 424*
- Phonocardiography, calibrated, 532*
- Phosphorus, radioactive, blood volume determinations with, 318*
- Plant, Robert K., and Steven, R. A., 615
- Plasma, dog, sulfadiazine, antitoxins, and globulins, effect of, on dogs in traumatic shock under sodium pentobarbital anesthesia, 106*
- Platt, Philip S., and Gunn, S. M., 425 (B. rev.)
- Pleune, F. G., Fink, K., Steadman, L. T., Warren, S. L., Scholz, D. E., and Schultz, J. H., 106*
- Pneumoperitoneum, electrocardiogram in, 579
- Poisoning, veronal, and infarct electrocardiogram, 632*
- Posture, alteration in P-R interval associated with change in, 109
an anxiety, normal values with observations on effect of; cardiac output in male subjects as measured by technique of right atrial catheterization, 315*
changes in, incomplete heart block produced by, 291
- Potassium thiocyanate used in treatment of hypertension, fatal poisoning from, 213*
- Powell, Vernon E., and Silverman, J. J., 441
- P-R interval, alteration in, associated with change in posture, 109
in rheumatic fever, provocative prolongation of, 104*
short, prolonged QRS complex, myocardial infarction superimposed on, 527
- Pressure, thoracic and abdominal, influence of, upon venous return in inferior vena cava, 315*
- Price, A. H., and Herbut, P. A., 211*
- Pruitt, R. D., Barnes, A. R., and Essex, H. E., 422*

Q

- Q waves, abnormal, differentiation of normal from, 341
- QRS complex, precordial, in normal subjects, normal mean zone of values of, 628*
prolonged, short P-R, myocardial infarction superimposed on, 527
- Quinidine lactate, observations on two patients with paroxysmal ventricular tachycardia treated by intravenous administration of, 276
- Quinine, treatment of night cramps and so-called vasomotor neurosis of extremities with, 632*

R

- Raah, W., 633*
- Ramos, J. G., and Rosenbluth, P. A., 314*
- Ray, Thiesen, and LaDue, J. S., 335
- Recrate, P., Duomarco, J., and Rimini, R., 315,* 420*
- Reed, Lewis K., and Berger, K. E., 622
- Rehm, W. S., and Lawson, H., 534,* 535,* 627*

- Respiration and circulation in arteriovenous aneurysm, modification of, 211*
- Respiratory system manifestations of neuro-circulatory asthenia; studies concerning etiology and pathogenesis of neurocirculatory asthenia, 557
- Rest, bed, effect of, on blood volume of normal young men, 631*
- Rheumatic fever activity and salicylate, 632*
- acute, prevention of, 424*
- erythrocyte sedimentation rate in, its significance in adolescent and overweight children, 533*
- in children, salicylate therapy in, 424*
- observations on salicylate therapy in, 424*
- provocative prolongation of P-R interval in, 104*
- relationship of postscarlatinal arthritis and carditis to, 629*
- Rhythm, so-called systolic gallop, nature and origin of, 423*
- Ricca, R. A., Warren, S. L., and Katzin, L. I., 106*
- , —, —, and Fink, K., 213*
- , —, Fink, K., and Steadman, L. F., 213*
- Rich, A. R., 632*
- Rimini, R., Recrate, P., and Duomarco, J., 315,* 420*
- Robbins, S. L., 209*
- Roberts, Joseph T., and Yater, W. M., 390
- Rodriguex, G. C., Del Solar, A. V., Dussailant, G. G., and Brodsky, M. B., 213*
- Roger's disease (*See* Septum, defect of)
- Rojas, R. A., Sabathie, L. G., and Gaspary, F. V., 422*
- Roos, A., 238
- Rose, D. L., Gotschall, R. Y., Laurent, D., DeKruif, P., Simpson, W. M., and Kendell, H. W., 536*
- Rosenbaum, Francis F., Wilson, F. N., and Johnston, F. D., 11
- Rosenblatt, P., and Loewe, L., 533*
- Rosenblueth, P. A., and Ramos, J. D., 314*
- Ross, A., and Keith, J. D., 424*
- Ross, G. T., Gregory, R., Ewing, P. L., and Levin, W. C., 630*
- Rothbard, S., Swift, H. F., and Watson, R. F., 629*
- Rubella, complete heart block in, 205
- Rundles, W. R., 534
- Russek, Henry I., and Zohman, B. L., 427
- S
- Sabathie, L. G., and Gaspary, F. V., 102*
- , —, and Rojas, R. A., 422*
- Sacks, David R., and Zoll, P. M., 527
- Saland, Gamliel, and Calef, B., 398
- Salicylate and rheumatic activity, 632*
- therapy in rheumatic fever, observations on, 424*
- in children, 424*
- Sapeika, Norman, and Berk, L., 365
- Saphir, O., 628*
- Sax, Simon G., and Wells, A. H., 522
- Sayen, A., and Naide, M., 107*
- Schiff, I., Krause, F., Ginsburg, H. N., Katz, L. N., and Wise, W., 125
- Schill, E., 628*
- Scholz, D. E., Schultz, J. H., Pleune, F. G., Fink, K., Steadman, L. T., and Warren, S. L., 106*
- Schultz, J. H., Pleune, F. G., Fink, K., Steadman, L. T., Warren, S. L., and Scholz, D. E., 106*
- Schwartz, Irving, Friedman, B., and Simard, E. E., 299
- Sedimentation rate, erythrocyte, effect of exercise upon, 627*
- in rheumatic fever, its significance in adolescent and overweight children, 533*
- in vitro, effect of sodium salicylate on, 533*
- Segall, Harold N., 39
- Seligman, A. M., Fine, J., and Frank, H. A., 535*
- Selzer, A., 631*
- Septum, intact interventricular, pulmonary stenosis with, 491
- interventricular, defect of (Roger's disease), occurring in mother and her six-month fetus, 54
- involvement of, and complete and incomplete transmural involvement, electrocardiographic features of myocardial infarction as affected by, 367
- large interauricular, defect of, with particular reference to diagnosis and longevity, 103*
- Shapiro, Robert, 88
- Shipley, R. E., and Gregg, D. E., 101*
- Shock, experimental traumatic, in dogs, effect of environmental temperature on, 213*
- following bilateral venous occlusion of hind-limbs of dog, observations on, 212*
- hemorrhagic, intestinal absorption in, 536*
- irreversible, failure of transfusions in, 319*
- to replacement of blood volume deficiency, treatment of, 535*
- pleural, transient heart block and coronary occlusion in, 423*
- produced by continuous intravenous injection of adrenalin, with or without anesthesia, study of body temperature and water content in, 106*
- tourniquet, distribution of body fluids of dogs in, 213*
- in rabbits, effect of environmental temperature and anesthesia on survival of, 106*
- in rats, thiamine-deficient diet in, 106*
- role of decompensatory reactions of peripheral blood vessels in, 212*
- traumatic; X. Treatment of hemorrhagic shock irreversible to replacement of blood volume deficiency, 535*

Shock, traumatic—Cont'd

- XI. Intestinal absorption in hemorrhagic shock, 536*
 under sodium pentobarbital anesthesia, effect of sulfadiazine, antitoxins, globulins, and dog plasma on dogs in, 106*
- Shore, R., Holt, J. P., and Knoefel, P. K., 420*
- Sigler, Louis H., 459
- Silverman, Jacob J., and Powell, V. E., 441
- Simard, Ernest E., Friedman, B., and Schwartz, I., 299
- Simon, Helmuth, Field, M. H., and Donovan, M. A., 230
- Simonson, E., and Enzer, N., 208*
- , —, and Goodman, J. S., 209*
- Simpson, W. M., Kendell, H. W., Rose, D. L., Gottschall, R. Y., Laurent, D., and DeKruif, P., 536*
- Sisson, J. H., Murphy, G. E., and Newman, E. V., 209*
- Situs inversus and dextrocardia, angina pectoris associated with, 202
- Smith, J. R., and Henry, M. J., 212*
- Smithwick, Reginald H., Mathews, M. W., Evans, E., and White, P. D., 165
- Sodium salicylate, effect of, on sedimentation rate of erythrocytes in vitro, 533*
 in cardiovascular rheumatism, value of iontophoresis with, 633*
- Soldiers, precordial pain in, strain of pectoralis minor muscle, an important cause of, 123
- Spuhler, O., and Holzmann, M., 632*
- S-T segment, ascending; its clinical importance, 208*
- Stead, E. A., Jr., Brannon, E. S., Merrill, A. J., and Warren, J. V., 315,* 420,* 421*
- Steadman, L. T., Warren, S. L., Fink, K., and Ricca, R. A., 213*
- , —, —, Scholz, D. E., Schultz, J. H., and Pleune, J. H., 106*
- Stein, Isidore, and Barber, J., 118
- Steinberg, F., and Jensen, J., 633*
- Steven, Robert A., 411
- , and Plant, R. K., 615
- Stewart, C. B., and Manning, G. W., 109
- Stewart, Harold J., Haskell, H. S., and Brown, H., 541
- Strain of pectoralis minor muscle, an important cause of precordial pain in soldiers, 123
- Straub-Fuehner frog heart preparation, effect of modulated high-frequency condenser field on, 420*
- Streptococci, Group A, *Streptococcus viridans*, and enterococci, effect of temperature elevation on action of sulfathiazole upon endocarditis strains of (II); pathology and bacteriology of streptococcus endocarditis in relationship to sulfonamide chemotherapy, 104*

Streptococci—Cont'd

- isolated from subacute bacterial endocarditis, note on serologic classification of, 511
- Strophanthus products and digitalis, present status of standardization of, in Canada, 633*
- Stroud, W. D., Hillman, C. C., Levy, R. L., and White, P. D., 534*
- Suarez, J. R. E., and Taquini, A. C., 211*
- Sulfadiazine, antitoxins, globulins, and dog plasma, effect of, on dogs in traumatic shock under sodium pentobarbital anesthesia, 106*
- Sulfonamide chemotherapy, pathology and bacteriology of streptococcus endocarditis in relationship to; I. Development of laboratory technique for study of chemotherapy in vitro, 104*
 II. Effect of temperature elevation on action of sulfathiazole upon endocarditis strains of *Streptococcus viridans*, enterococci, and Group A streptococci, 104*
 origin, isolated myocarditis probably of, 522
- Sulzer, R., and Duchosal, P. W., 532*
- Swift, H. F., Watson, R. F., and Rothbard, S., 629*
- Sympathectomy, primary influence of basal vascular tone on development of postocclusive collateral circulation and in selecting patients for, 107*
 radical lumbodorsal, effect of (II); electrocardiogram in hypertension, 165
- Syndrome of Bernheim, 427
- Stokes-Adams, treated with parendrine, acute rheumatic heart disease in aged, with report of a case with, 415
- Syphilis, early, electrocardiographic changes in, prior to and upon completion of intensive arsenotherapy, 551
- Szucs, M., Ungerleider, H. E., and Gubner, R., 104*
- T
- T deflection of electrocardiogram, effect of cycle-length changes upon form and amplitude of, 208*
- T wave, downward, of electrocardiogram, effects of amyl nitrite on, 60
- Tachycardia, nervous tension, and normal or elevated popliteal pressure, transient "0" diastolic brachial pressure (indirect), associated with, 381
- paroxysmal, electrocardiograms simulating posterior myocardial infarction after cessation of, 401
- ventricular, observations of two patients with, treated by intravenous administration of quinidine lactate, 276

- Talesnik, J., Hoffmann, F., Hoffmann, E. J., and Middleton, S., 627*
- Taquini, A. C., and Lozada, B., 208*
- , and Suarez, J. R. E., 211*
- Taran, L. M., and Jacobs, M. H., 424*
- Taussig, H. B., 209*
- Taylor, H. L., Erickson, L., Henschel, A., and Keys, A., 631*
- Telangiectasia, hemorrhagic, with pulmonary artery aneurysm, 534*
- Temperature elevation, effect of, on action of sulfathiazole upon endocarditis strains of *Streptococcus viridans*, enterococci, and Group A streptococci (II); pathology and bacteriology of streptococcus endocarditis in relationship to sulfonamide chemotherapy, 104*
- environmental, and anesthesia, effect of, on survival of tourniquet shock in rabbits, 106*
- effect of, on experimental traumatic shock in dogs, 213*
- Theophylline, aminoisobutanol in angina pectoris, on use of, 633*
- effect of, with ethylenediamine (aminophylline) and of papaverine hydrochloride on experimental myocardial infarction in dog, 215
- Thiouracil, diminution of epinephrine sensitivity of normal human heart through, 633*
- therapy, pericarditis and complete heart block during, 107*
- Thrombosis and arterial embolism in infancy, 631*
- Thrombotic or embolic processes, incidence of, during immediate convalescence from acute myocardial infarction, 65
- Transfusions in irreversible hemorrhagic shock, failure of, 319*
- Trauma of heart, 622
- Traumatic injury of heart, incidence of its occurrence in forty-two cases of severe accidental bodily injury, 459
- Tucker, Arthur W., and Kinney, T. D., 54
- Tumor, primary, of left auricle simulating mitral stenosis, 230
- secondary, of heart, diagnosed at operation, 630*

U

- Ungerleider, H. E., Gubner, R., and Szucs, M., 104*

V

- Valentine, William N., and Nicholl, R. J., 514
- Valve, calcareous aortic stenosis of, relative incidence of rheumatic valve disease in New York and Costa Rica and its bearing on rheumatic origin of, 573
- mitral, annulus fibrosus calcification of, 619
- stenosis, advanced, at 3 years old, 210*
- primary tumor of left auricle simulating, 230

Valve—Cont'd

- pulmonary, stenosis of, with intact interventricular septum, 491
- Vascular system, arteriosclerotic peripheral, disease in diabetes, 630*
- peripheral, changes in dermatomyositis, 441
- disease of, evaluation of vascular reserve in, 398
- tone, basal, primary influence of, on development of postocclusive collateral circulation and in selecting patients for sympathectomy, 107*
- Vector AvT in ventricular hypertrophy, six axis system with application to, 208*
- Vena cava, inferior, influence of abdominal and thoracic pressure upon venous return in, 315*
- Venesection and pooling of blood in extremities, effect of, on atrial pressure and cardiac output in normal subjects with observations on acute circulatory collapse in three instances, 421*
- for plethoric patient, 213*
- Ventricle, cardiac, interpretation of electrogram of, 314*
- hypertrophy of, six axis system with application to vector AvT in, 208*
- Ventricles, both, of heart, traumatic rupture of, 519
- Veronal poisoning and infarct electrocardiogram, 632*
- Visscher, Maurice B., and Henschel, A., 592
- Vizcaino, M., Pallarés, D. S., and Cabrera, E., 421*

W

- Waldman, Samuel, 92
- Warneford-Thomson, Hugo F., White, P. D., and Canabal, E. J., 189
- Warren, J. F., Merrill, A. J., Brannon, E. S., and Stead, E. A., Jr., 315,* 420,* 421*
- Warren, S. L., and Katzin, L. I., 106*
- , —, and Ricca, A. R., 106*
- , —, —, and Fink, 213*
- , Ricca, R. A., and Fink, K., 106*
- , —, —, and Steadman, L. T., 213*
- , Scholz, D. E., Shultz, J. H., Pleune, F. G., Fink, K., and Steadman, L. T., 106*
- Water content and body temperature in shock produced by continuous intravenous injection of adrenalin, with or without anesthesia, study of, 106*
- Watson, R. F., Rothbard, S., and Swift, H. F., 629*
- Wedd, A. M., and Blair, H. A., 633*
- Weill, David R., Jr., and Holmes, J. H., 291
- Weinroth, L. A., and Herzstein, J., 630*
- Weisiger, J. R., and Moritz, A. R., 101*
- Wells, Arthur H., and Sax, S. G., 522
- Wheeler, S. M., and Foley, G. E., 511
- White, P. D., and Burrett, J. B., 103*

- , Canabal, E. J., and Warneford-Thomson, H. F., 189
- , Currens, J. H., and Kinney, T. D., 491
- , Evans, E., and Mathews, M., 140
- , —, —, and Smithwick, R. H., 165
- , Stroud, W. D., Hillman, C. C., and Levy, R. L., 534*
- Wiggers, C. J., 319*
- Wilburne, Morris, 381
- Wilens, Sigmund L., Pearce, J. M., and Diaz, M. F., 573
- Wilson, Frank N., Johnston, F. D., and Rosenbaum, F. F., 11
- Wilson, K. S., and Alexander, H. L., 210*
- Winsor, Travis, and Burch, G., 537 (B. rev.)
- Wise, W., Katz, L. N., and Jochim, K., 105,* 211,* 317*
- , —, Ginsburg, H. N., Schiff, I., and Krause, F., 125
- Woodall, Paul S., and Monto, R. W., 519
- Work, physical, influence of aging in man upon his capacity for, and upon his cardiovascular responses to exercise, 102*
- Wounds of major blood vessels of lower extremity, experience with lumbar sympathetic ganglionectomy for, 534*
- Wright, Willis D., and Niehaus, F. W., 604
- Y
- Yater, Wallace M., and Roberts, J. T., 390
- Yépez, C. G., and Gómez, B. H., 422*
- Z
- Zohman, Burton L., and Russek, H. I., 427
- Zoll, Paul M., and Sacks, D. R., 527
- Zweifach, B. W., Abell, R. G., Chambers, R., and Clowes, G. H. A., 212

